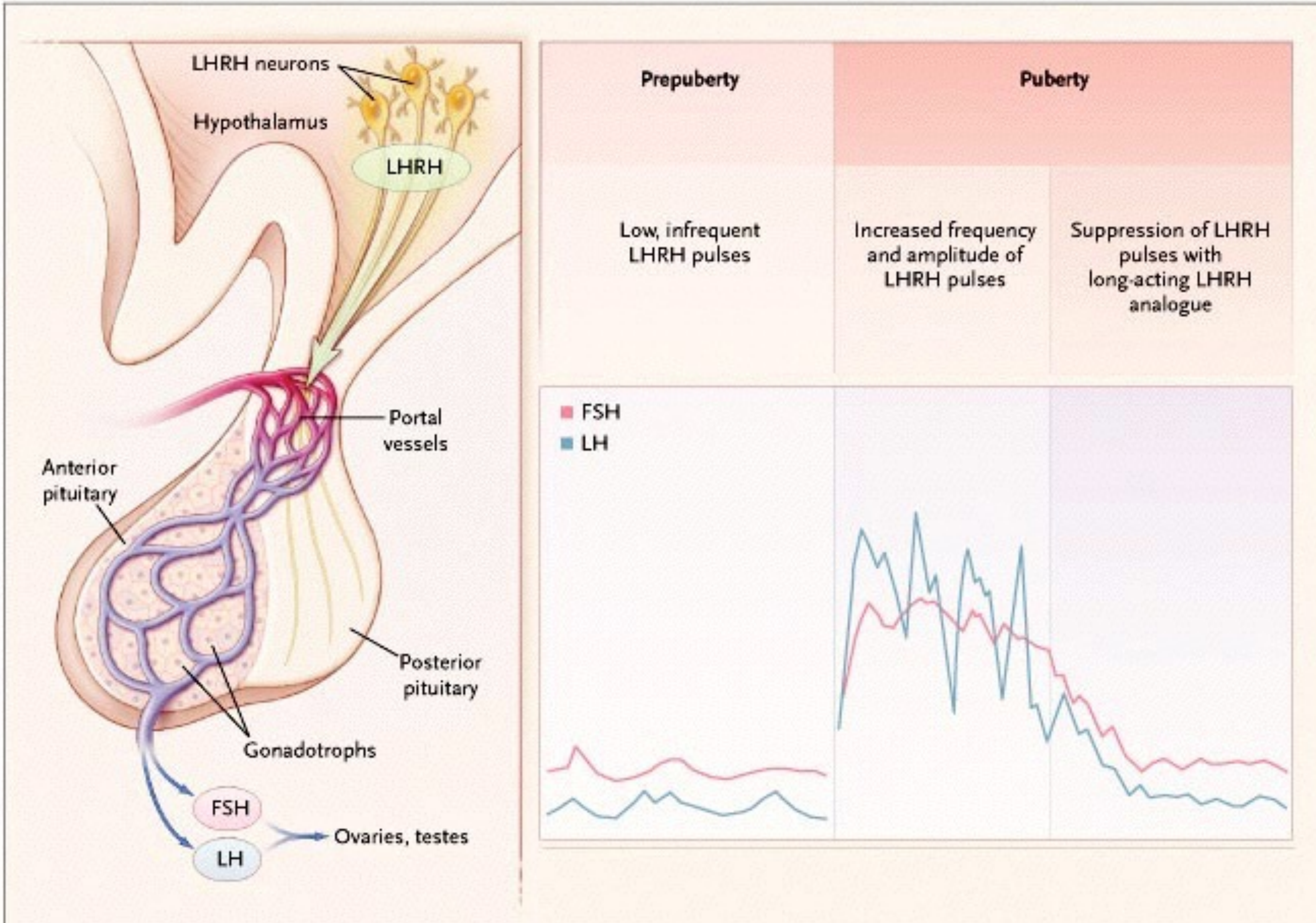
Pubertà normale

Aggiornamento 15 ottobre 2015

Pubertà

Inizia con la comparsa dei caratteri sessuali secondari e si completa in quattro anni circa con il raggiungimento della maturità funzionale delle gonadi e quindi della capacità di procreare.


LHRH neurons
Hypothalamus
LHRH
Portal vessels
Anterior pituitary
Posterior pituitary
Gonadotrophs
FSH
LH
Ovaries, testes
Prepuberty
Puberty
Low, infrequent LHRH pulses
Increased frequency and amplitude of LHRH pulses
Suppression of LHRH pulses with long-acting LHRH analogue
FSH
LH

Stadi dello sviluppo sessuale alla pubertà nelle femmine

(adattato da Marshall WA, Tanner JM. variations in the pattern of pubertal changes in girls. Arch Dis Child 1969; 44: 291-303)

P1 - prepuberale

P2 - iniziale comparsa di tumefazione sottoareolare mammaria; allargamento delle areole, con o senza comparsa di alcuni peli sulle grandi labbra e alle ascelle.

P3 - aumento palpabile delle dimensioni del tessuto mammario e delle areole; comparsa di discreta quantità di peli sessuali scuri al pube e incremento dei peli ascellari; comparsa di odore corporeo caratteristico.

P4 - Ulteriore incremento di volume delle mammelle e delle areole che sporgono oltre il livello del seno; peli pubici adulti come quantità, ma localizzati al Monte di Venere; acne e possibile comparsa di menarca.

P5 - dimensioni adulte di seno e areola, che ritorna allo stesso livello del seno con protrusione del capezzolo; distribuzione adulta del pelo pubico con estensione alla parte superiore delle cosce; menarca.

Stadi dello sviluppo sessuale alla pubertà nei maschi

(adattato da Marshall WA, Tanner JM. variations in the pattern of pubertal changes in boys.

Arch Dis Child 1970; 45: 13-23)

P1 - prepuberale; testicolo di lunghezza inferiore a 2,5 cm.

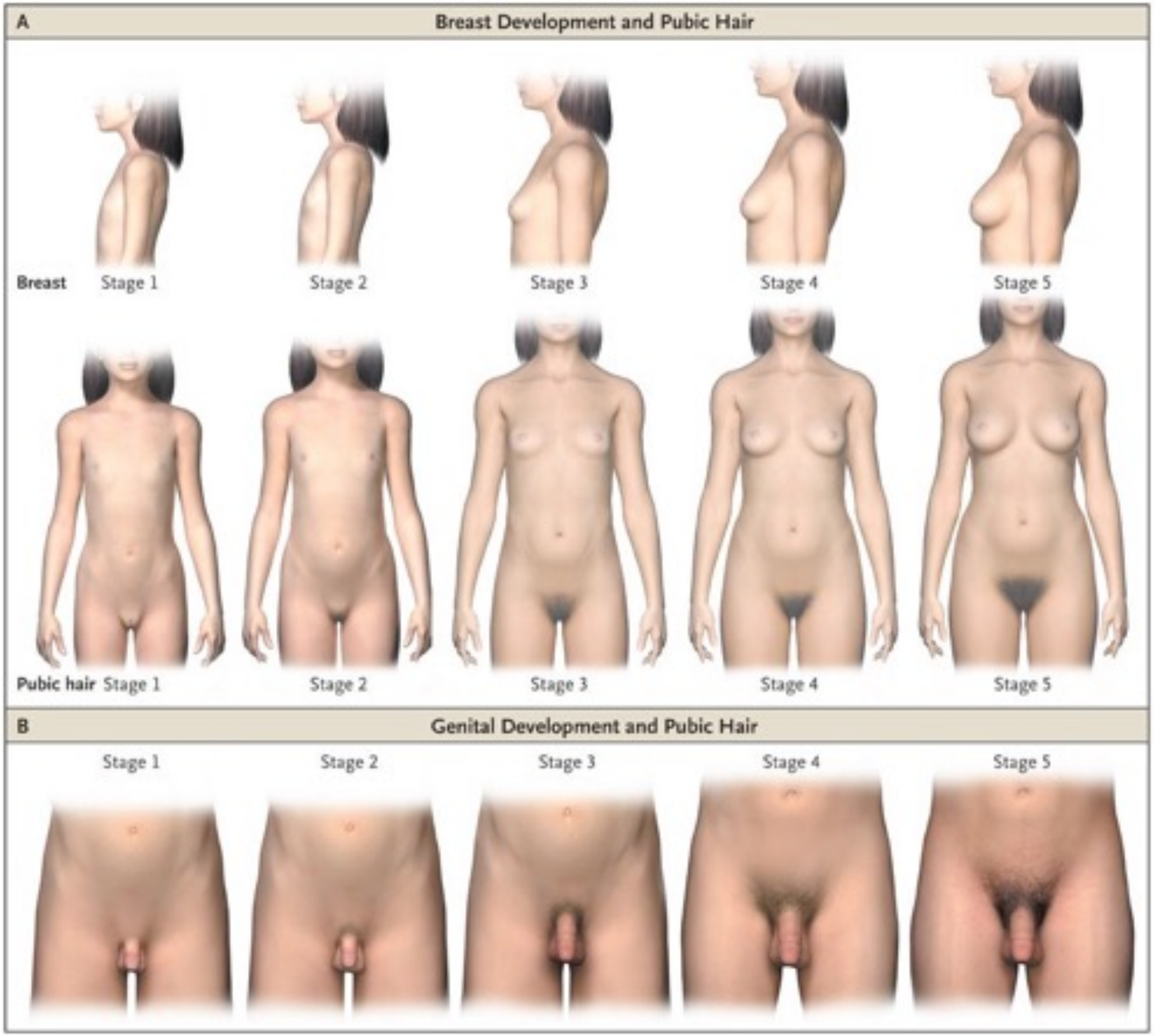
P2 - aumento precoce delle dimensioni dei testicoli (2,5-3,2 cm); iniziale pigmentazione dello scroto; pochi peli pubici o scrotali lunghi e scuri.

P3 - lunghezza del testicolo di 3,3-4,0 cm; iniziale allungamento del pene; aumento dei peli pubici, con o senza comparsa di peli ascellari.

P4 - testicoli con dimensioni di 4,1-4,5 cm; ulteriore aumento di lunghezza e ingrossamento del pene; peli pubici adulti come quantità, ma senza estensione verso l'ombelico, cosce e ano; aumento del pelo ascellare ed al corpo; comparsa di barba e baffi; comparsa del caratteristico odore del corpo; abbassamento del tono di voce; presenza di acne; eiaculazioni.

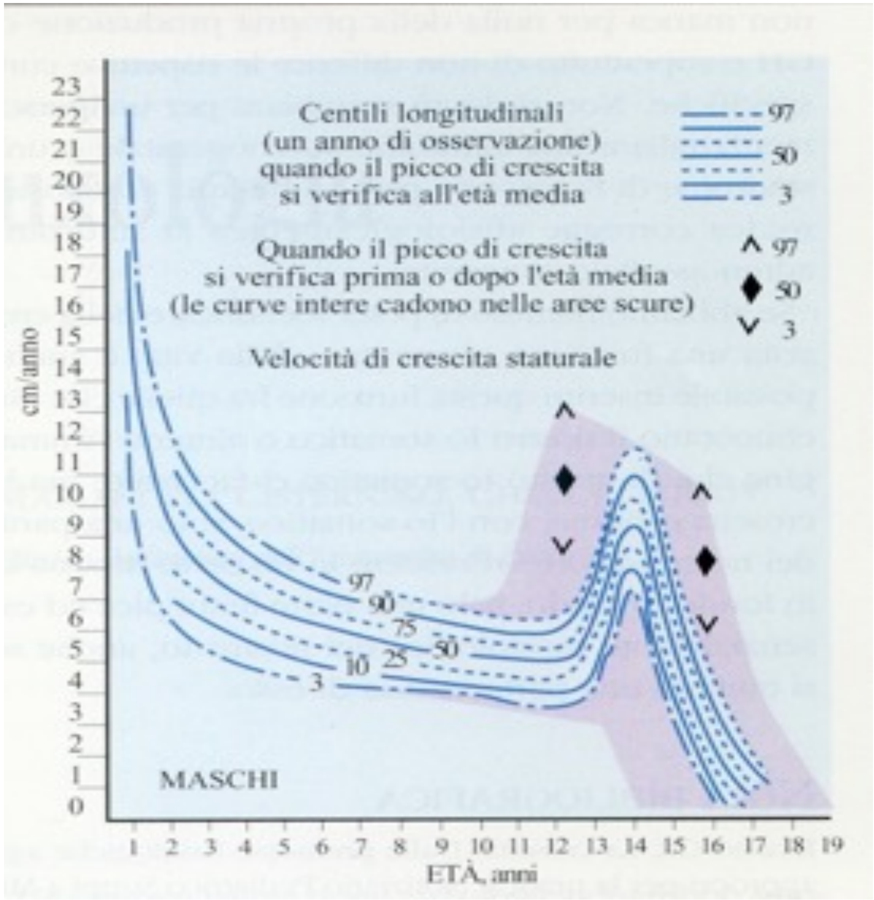
P5 - testicoli di lunghezza superiore ai 4,5 cm; genitali esterni di tipo adulto; peli sessuali con distribuzione caratteristica; spermatogenesi efficiente.

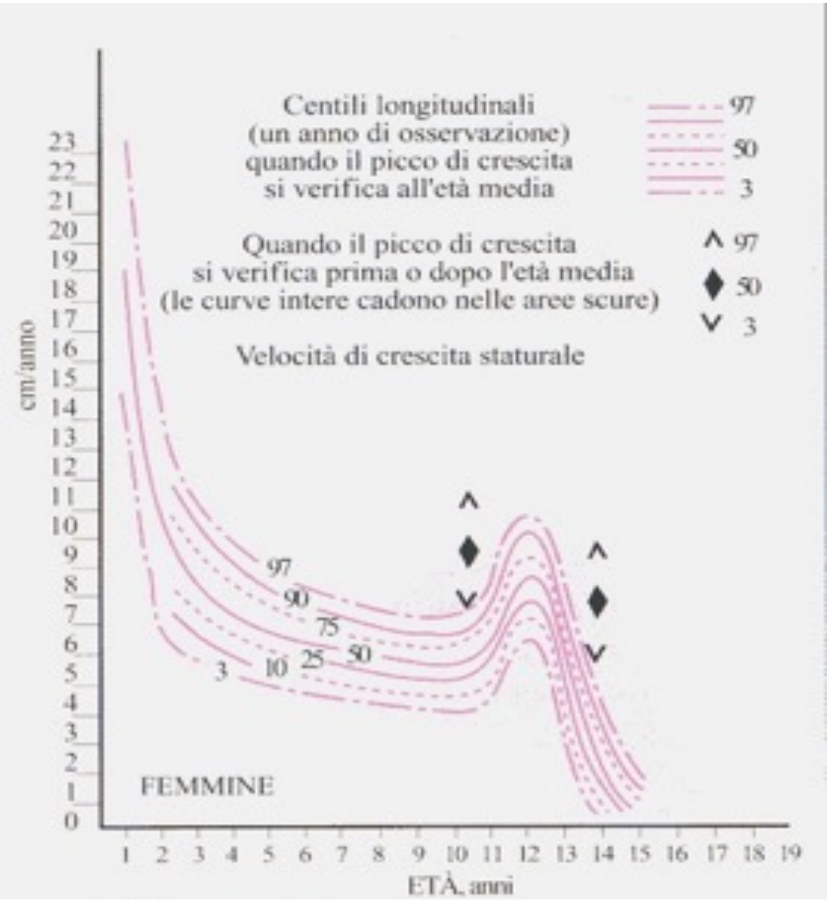
Pubertal Rating According to Tanner Stages



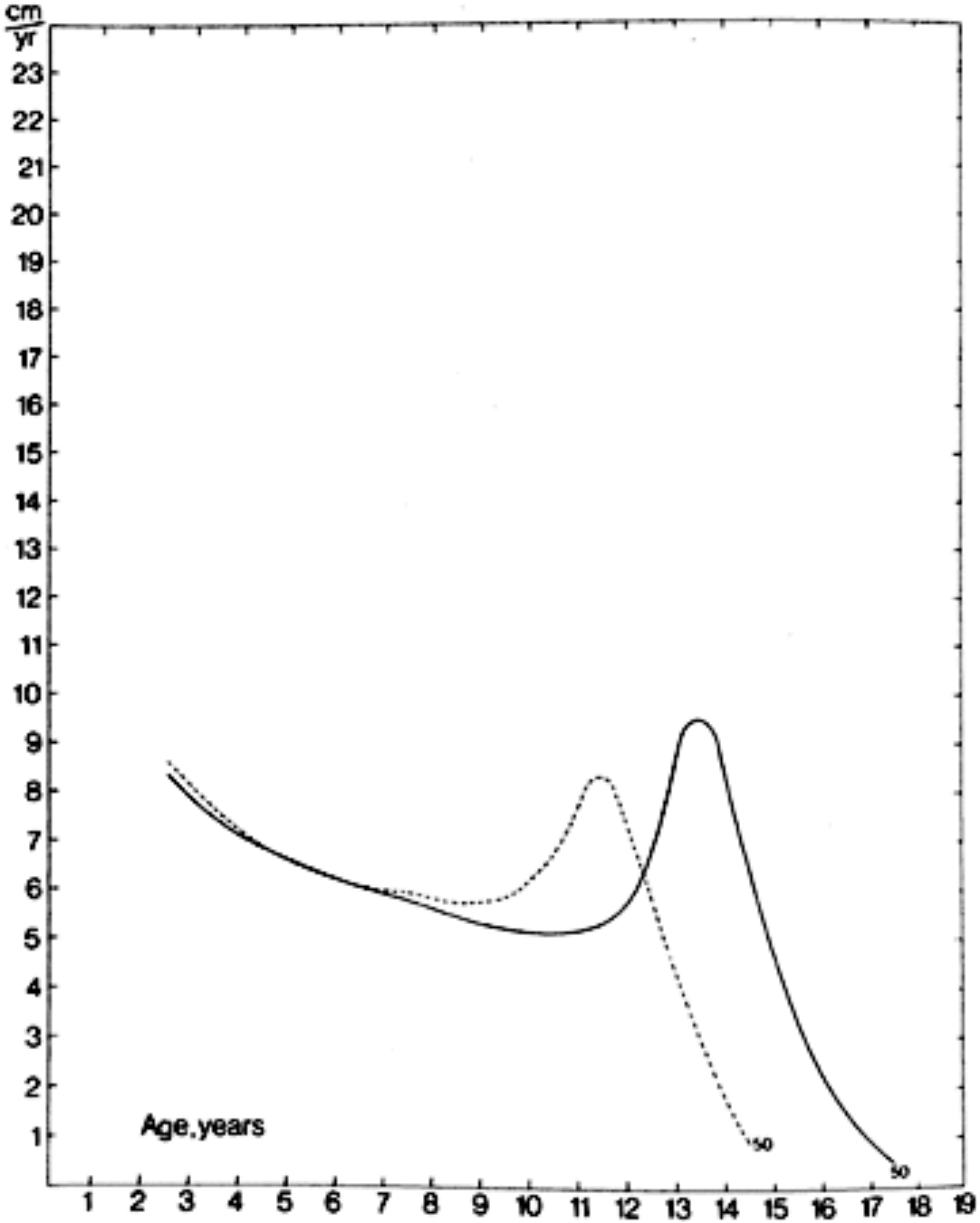
Carel J, Léger J. N Engl J Med 2008;358:2366-2377

Velocità di crescita





Pediatria Politematica - Crescita normale e patologica - UTET


cm/yr
23
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2
1
Age, years
50
50
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19

PROCESSI BIOLOGICI DELLA PUBERTA'

accelerazione e poi decelerazione dell'accrescimento staturale; cambiamento di proporzioni;

modificazione degli organi sessuali secondari, sviluppo delle gonadi e degli organi riproduttivi;

modificazioni della composizione corporea

- apparato scheletrico; massa ossea;
- apparato muscolare;
- distribuzione del grasso.

modificazioni del sistema circolatorio e respiratorio.

MODIFICAZIONI DELLA COMPOSIZIONE CORPOREA

Massa magra corporea:

- si riduce nelle femmine e aumenta nei maschi

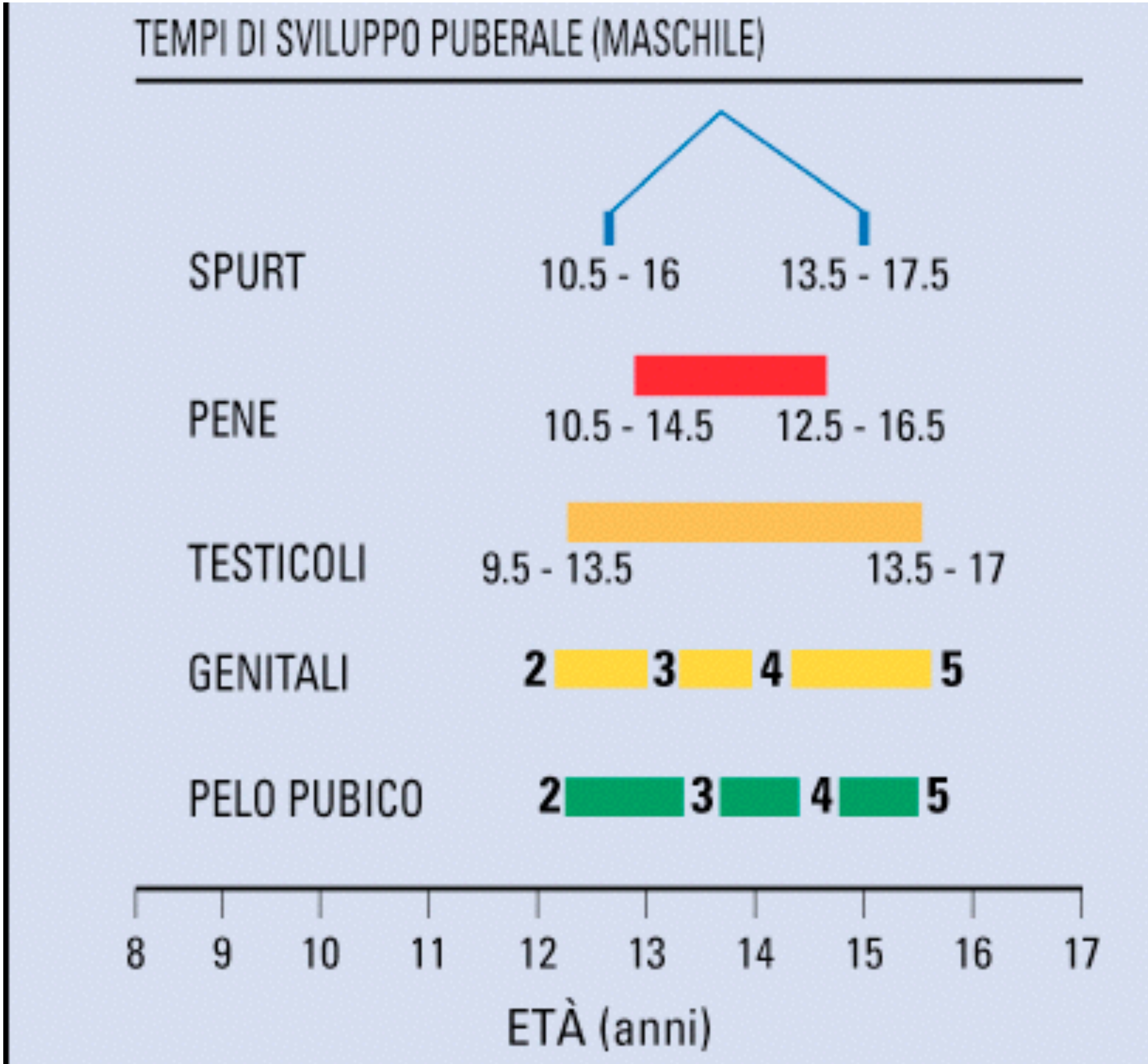
Massa adiposa:

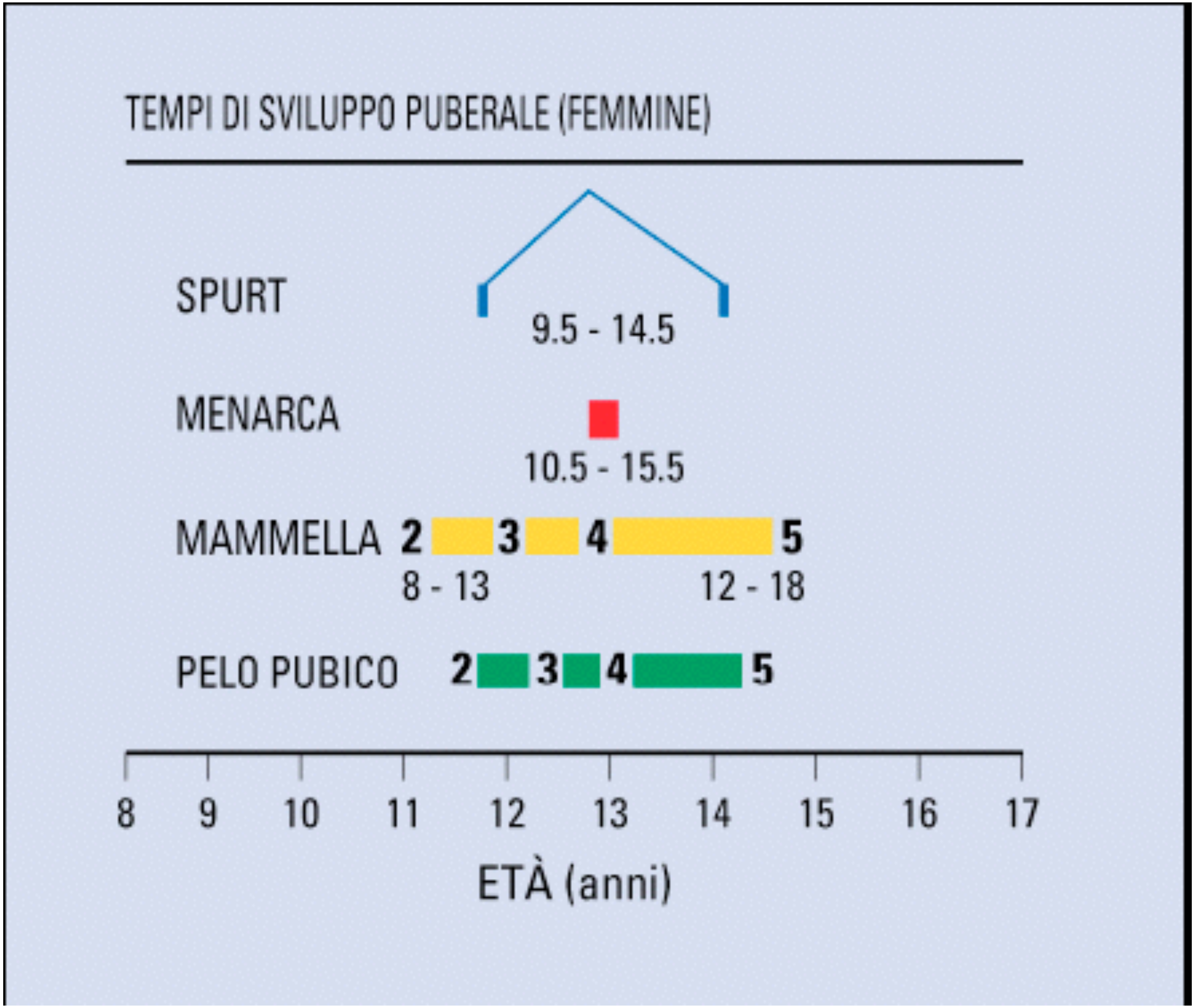
- aumenta nelle femmine e rimane costante nei maschi

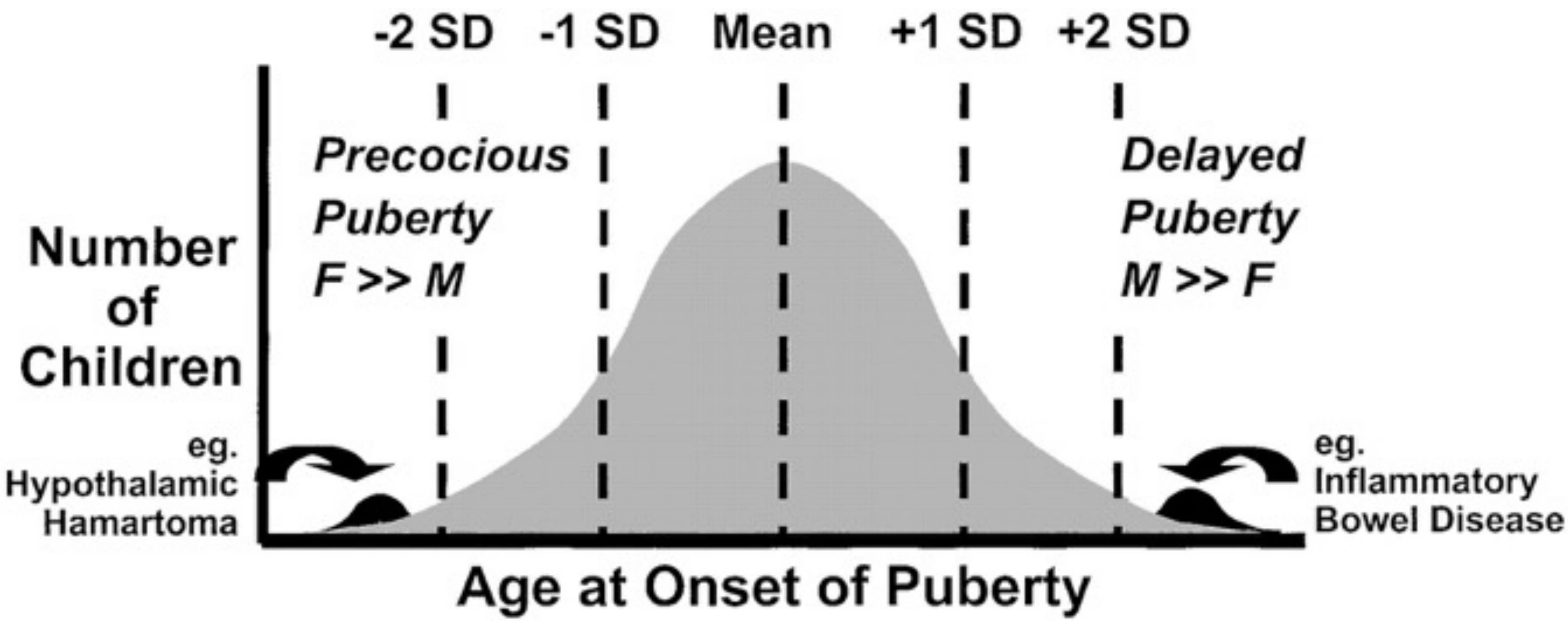
Massa ossea: netto incremento durante la pubertà fino a raggiungere il picco di massa ossea (peak bone mass)

- in relazione con l'epoca puberale, con fattori razziali, ormonali e con la supplementazione della dieta con calcio.

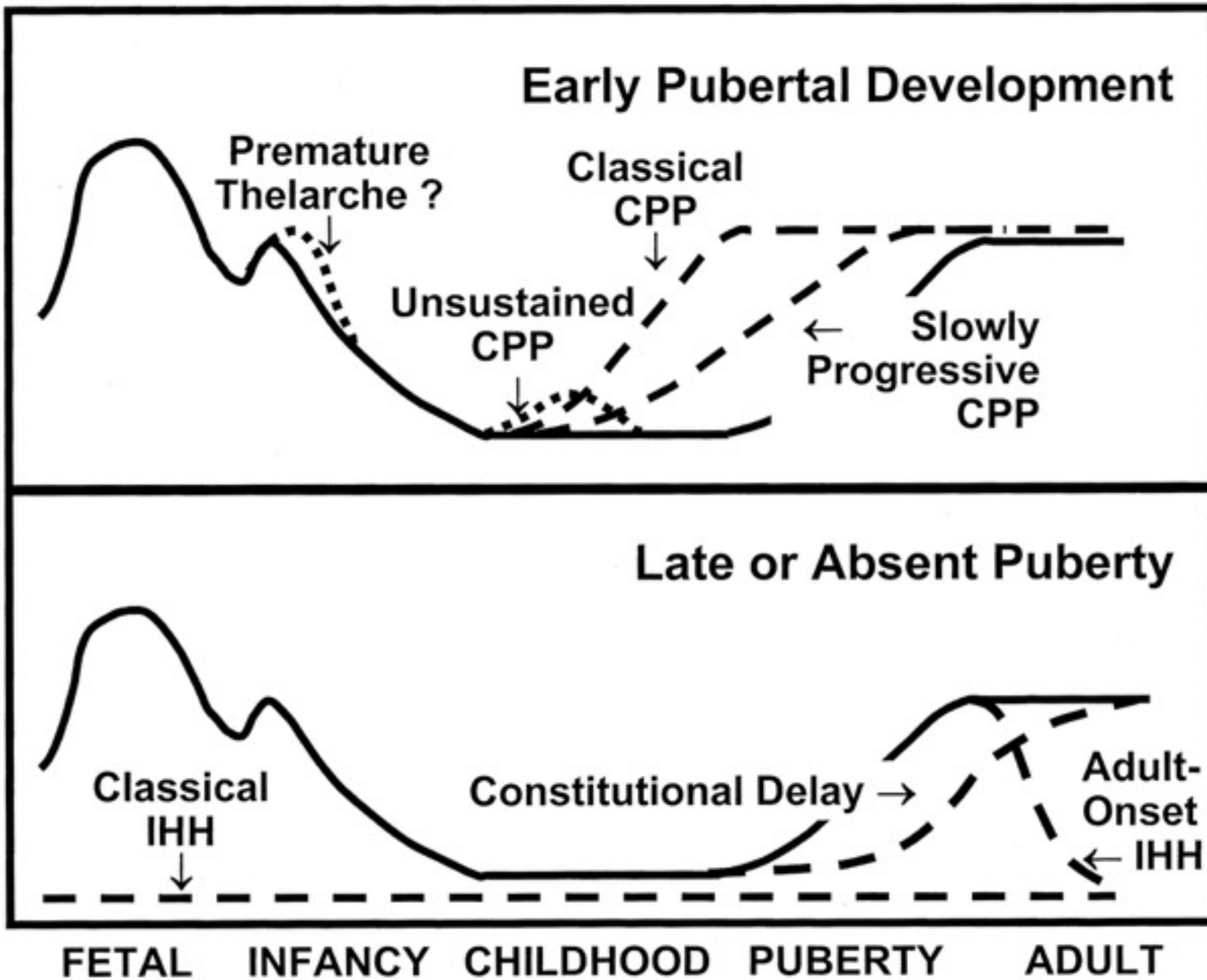
Modificazioni funzionali del sistema circolario e respiratorio:


TEMPI DI SVILUPPO PUBERALE (MASCHILE)
SPURT
10.5 - 16
13.5 - 17.5
PENE
10.5 - 14.5
12.5 - 16.5
TESTICOLI
9.5 - 13.5
13.5 - 17
GENITALI
2
3
4
5
PELO PUBICO
2
3
4
5
8
9
10
11
12
13
14
15
16
17
ETÀ (anni)


TEMPI DI SVILUPPO PUBERALE (FEMMINE)
SPURT
9.5 - 14.5
MENARCA
10.5 - 15.5
MAMMELLA
2
3
4
5
8 - 13
12 - 18
PELO PUBICO
2
3
4
5
8
9
10
11
12
13
14
15
16
17
ETÀ (anni)

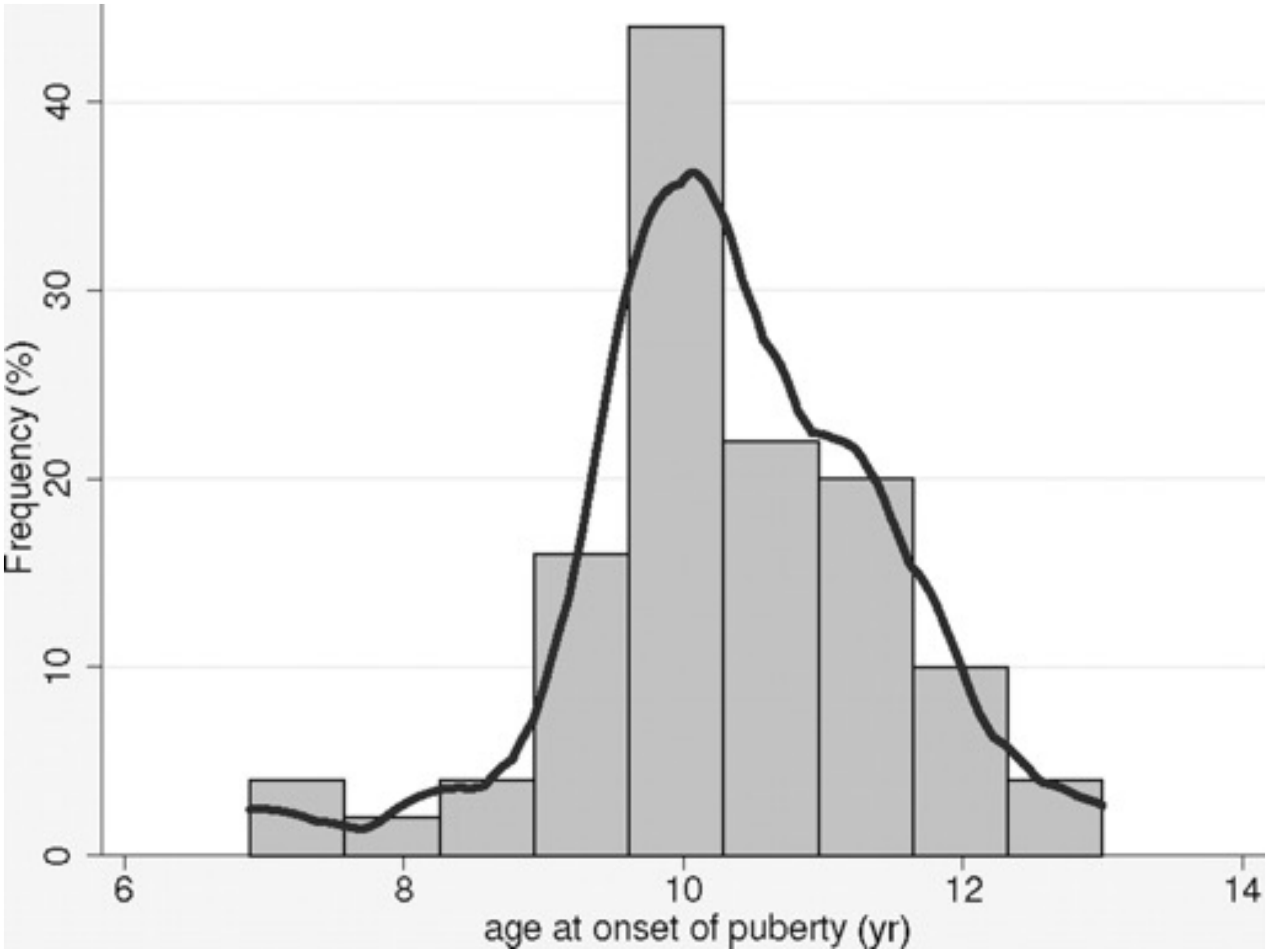


Palmert MR & Boepple PA. JCE&M 2001; 86: 2364–2368



Palmert MR & Boepple PA. JCE&M 2001; 86: 2364–2368

FIG. 2. Distribution of the age at onset of puberty in the cross-sectional study



Papadimitriou, A. et al. J Clin Endocrinol Metab 2008;93:4422-4425

The Journal of Clinical Endocrinology & Metabolism

Early menarcheal age has been shown in

- high socioeconomic status in developing countries
- low socioeconomic status and low level of education in modern Western countries
- childhood obesity
- lack of exercise in childhood
- high-conflict family relationships
- low birth weight
- singletons
- non-white
- experienced pre-eclampsia during pregnancy
- smoking
- not breast-fed
- migration
- child adoption from developing countries into Western families

Late menarcheal age has been shown in

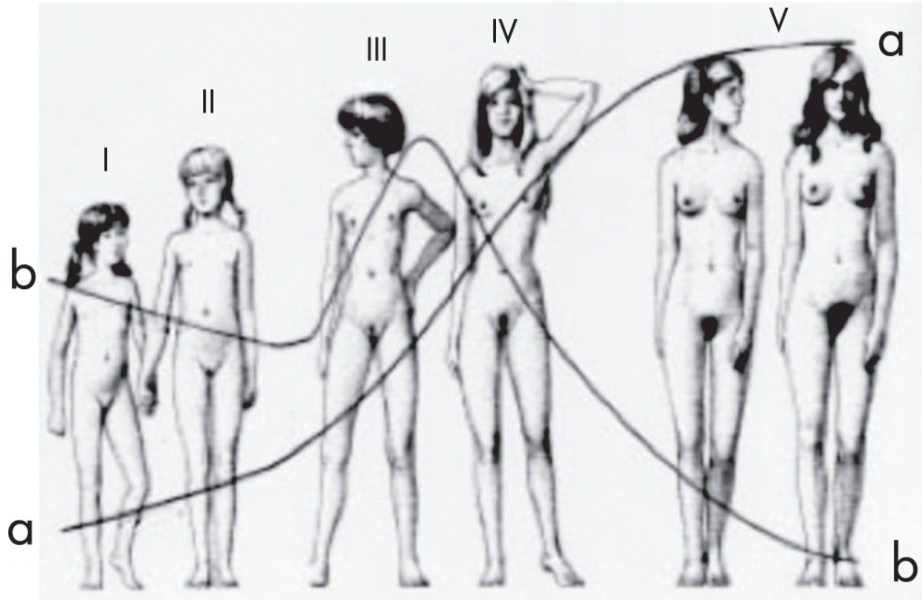
- low socioeconomic status and low level of education in developing countries
- malnutrition
- chronic illness
- psychological stress
- professional sport activity (e.g. gymnasts)
- social amenorrhea (▶ **7.5 The History of Menarcheal Age**)

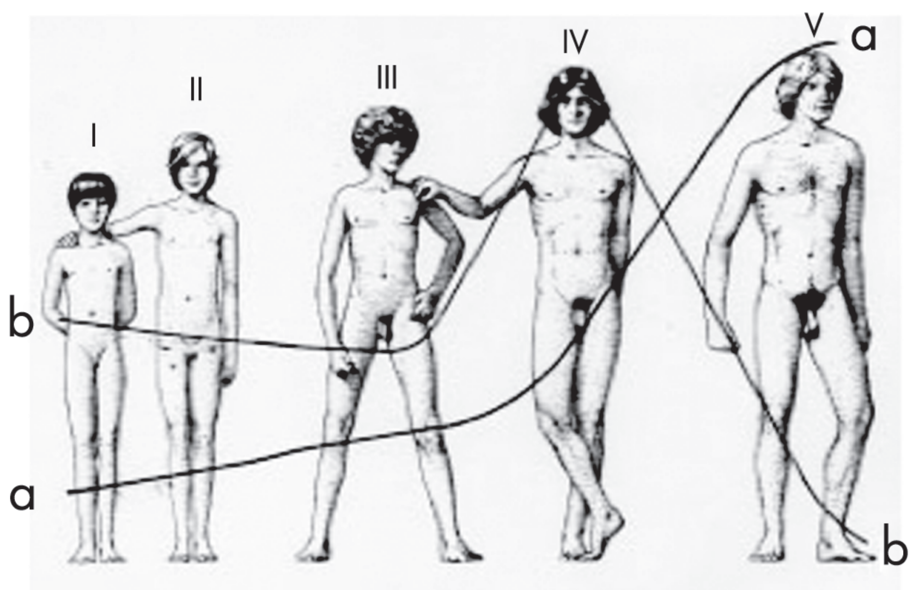
Pubertal Timing, Bone Acquisition, and Fracture Throughout Life

Jean-Philippe Bonjour and Thierry Chevalley

Division of Bone Diseases, University Hospitals and Faculty of Medicine, CH-1211 Gen

(*Endocrine Reviews* 35: 820–847, 2014)



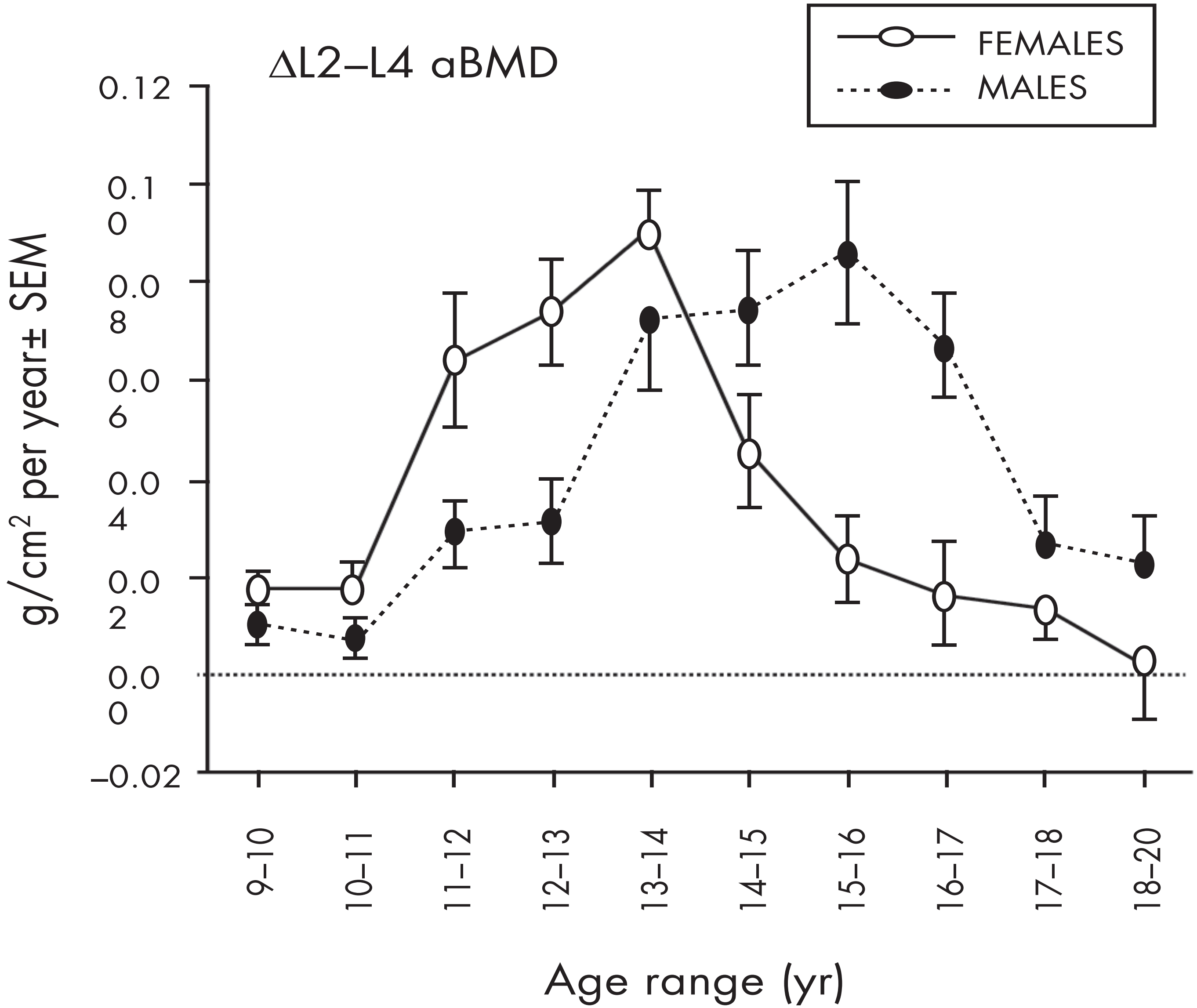


2014 Bonjour Puberty Bo

Pubertal Timing, Bone Acquisition, and Risk of Fracture Throughout Lif

Jean-Philippe Bonjour and Thierry Che
Division of Bone Diseases, University Hospitals and

(*Endocrine Review*



2014 Bonjour

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The GPR54 Gene as a Regulator of Puberty

Stephanie B. Seminara, M.D., Sophie Messager, Ph.D.,
Emmanouella E. Chatzidaki, B.Sc., Rosemary R. Thresher, Ph.D.,
James S. Acierno, Jr., B.S., Jenna K. Shagoury, B.S., Yousef Bo-Abbas, M.D.,
Wendy Kuohung, M.D., Kristine M. Schwinof, M.A., Alan G. Hendrick, Ph.D.,
Dirk Zahn, Ph.D., John Dixon, B.A., Ursula B. Kaiser, M.D.,
Susan A. Slaugenhaupt, Ph.D., James F. Gusella, Ph.D., Stephen O'Rahilly, M.D.,
Mark B.L. Carlton, Ph.D., William F. Crowley, Jr., M.D.,
Samuel A.J.R. Aparicio, B.M., B.Ch., Ph.D., and William H. Colledge, Ph.D.

Mutations in GPR54,a G protein-coupled receptor gene, cause autosomal recessive idiopathic hypogonadotropic hypogonadism in humans and mice, suggesting that this receptor is essential for normal gonadotropin-releasing hormone physiology and for puberty

Seminara SB et Al. NEJM 2003; 349: 1614-27

DE GRUYTER DOI 10.1515/jpem-2013-0080 — J Pediatr Endocr Met 2013; aop

Letter to the Editor

Marina Krstevska-Konstantinova, Jana Jovanovska, Velibor B. Tasic, Luciana Ribeiro Montenegro, Daiane Beneduzzi, Leticia F.G. Silveira and Zoran S. Gucev*

Mutational analysis of *KISS1* and *KISS1R* in idiopathic central precocious puberty

2013 Krstevska-Konstantinova PP Kisspeptin

A new pathway in the control of the initiation of puberty: the *MKRN3* gene

Ana Paula Abreu, Delanie B Macedo[1], Vinicius N Brito[1], Ursula B Kaiser and **Ana Claudia Latronico[1]**

Division of Endocrinology, Diabetes and Hypertension, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts, USA
[1]Unidade de Endocrinologia do Desenvolvimento, Disciplina de Endocrinologia e Metabologia, Laboratório de Hormônios e Genética Molecular, LIM 42, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Avenida Dr Enéas de Carvalho Aguiar, 255, 7° andar, sala 7037, CEP: 05403-900, São Paulo, Brazil

Correspondence should be addressed to A C Latronico
Email
anacl@usp.br

2015 Abreu PP MKRN3

Review | A P Abreu and others | *MKRN3 deficiency causes CPP* | **54**:3 | **R131**–R139

A new pathway in the control of the initiation of puberty: the *MKRN3* gene

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[1]Unidade de Endocrinologia do Desenvolvimento, Disciplina de Endocrinologia e Metabologia, Laboratório de Hormônios e Genética Molecular, LIM 42, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Avenida Dr Enéas de Carvalho Aguiar, 255, 7° andar, sala 7037, CEP: 05403-900, São Paulo, Brazil

Correspondence should be addressed to A C Latronico
Email
anacl@usp.br

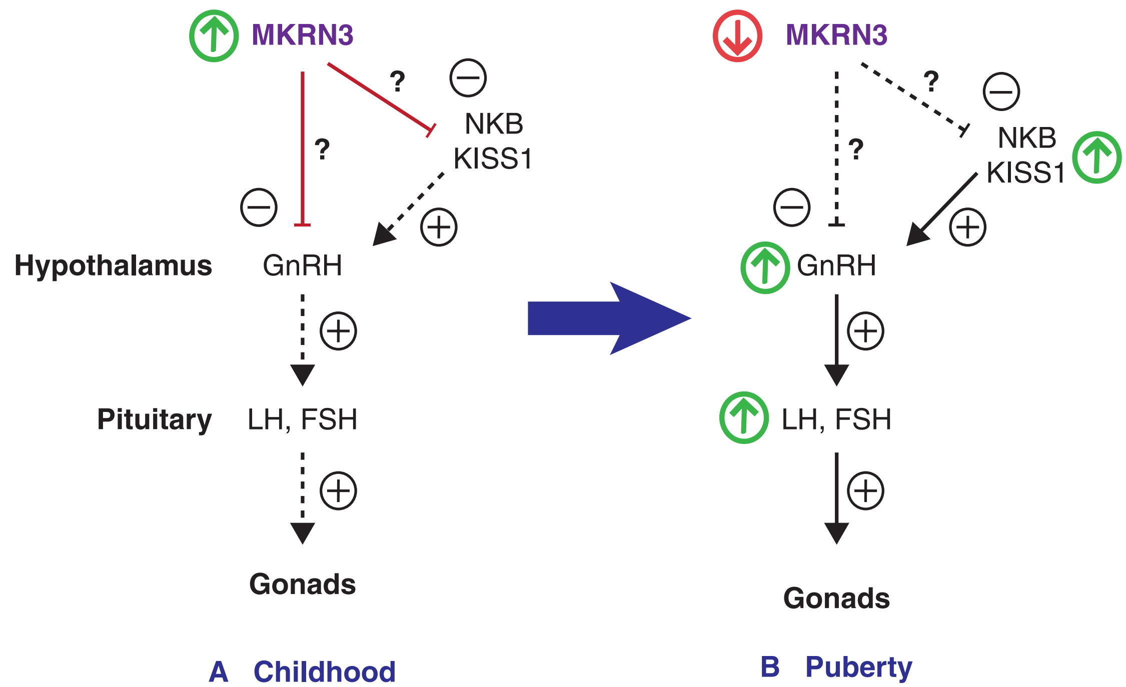

Figure 3
Schematic representation of MKRN3 mechanism of action. Human and mouse studies suggest that MKRN3 acts as an inhibitor of GnRH secretion during childhood (diagram on A), and that a decrease in *MKRN3* expression is associated with an increase in GnRH stimulatory factors and/or GnRH resulting in puberty initiation (diagram on B). NKB, neurokinin B; − inhibition, + stimulation. ↑ increase ↓ decrease.

2015 Abreu PP MKRN3

doi:10.1038/nature13545

Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche

A list of authors and their affiliations appears at the end of the paper

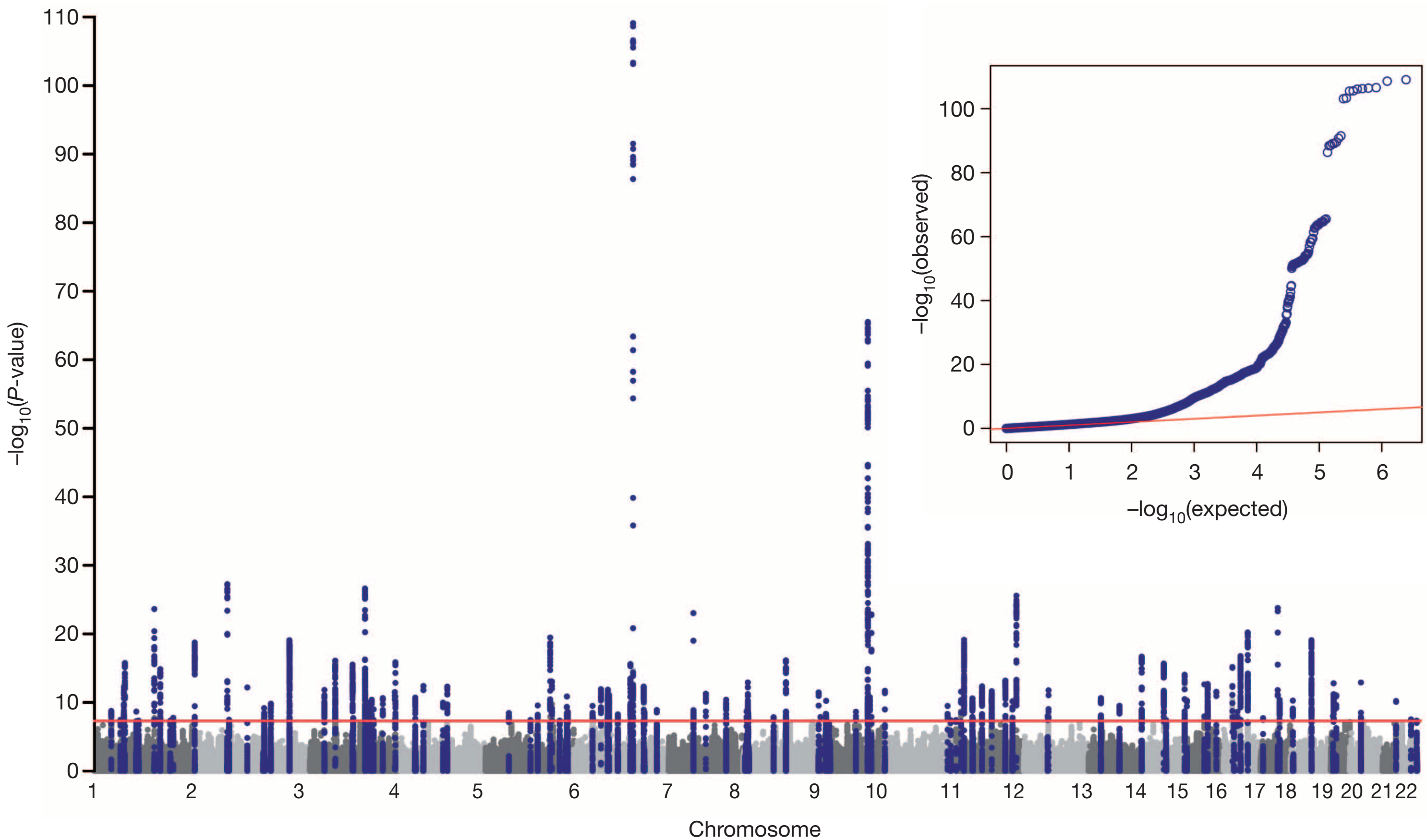

Figure 1 | Manhattan and quantile–quantile plot of the GWAS for age at menarche. Manhattan (main panel) and quantile–quantile (QQ) (embedded) plots illustrating results of the genome-wide association study (GWAS) meta-analysis for age at menarche in up to 182,416 women of European descent. The Manhattan plot presents the association $-\log_{10}(P\text{-values})$ for each genome-wide SNP (y axis) by chromosomal position (x axis). The red line indicates the threshold for genome-wide statistical significance ($P = 5 \times 10^{-8}$). Blue dots represent SNPs whose nearest gene is the same as that of the genome-wide significant signals. The QQ plot illustrates the deviation of association test statistics (blue dots) from the distribution expected under the null hypothesis (red line).

2014 AAVV Genetics Menarche

doi:10.1038/nature13545

Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche

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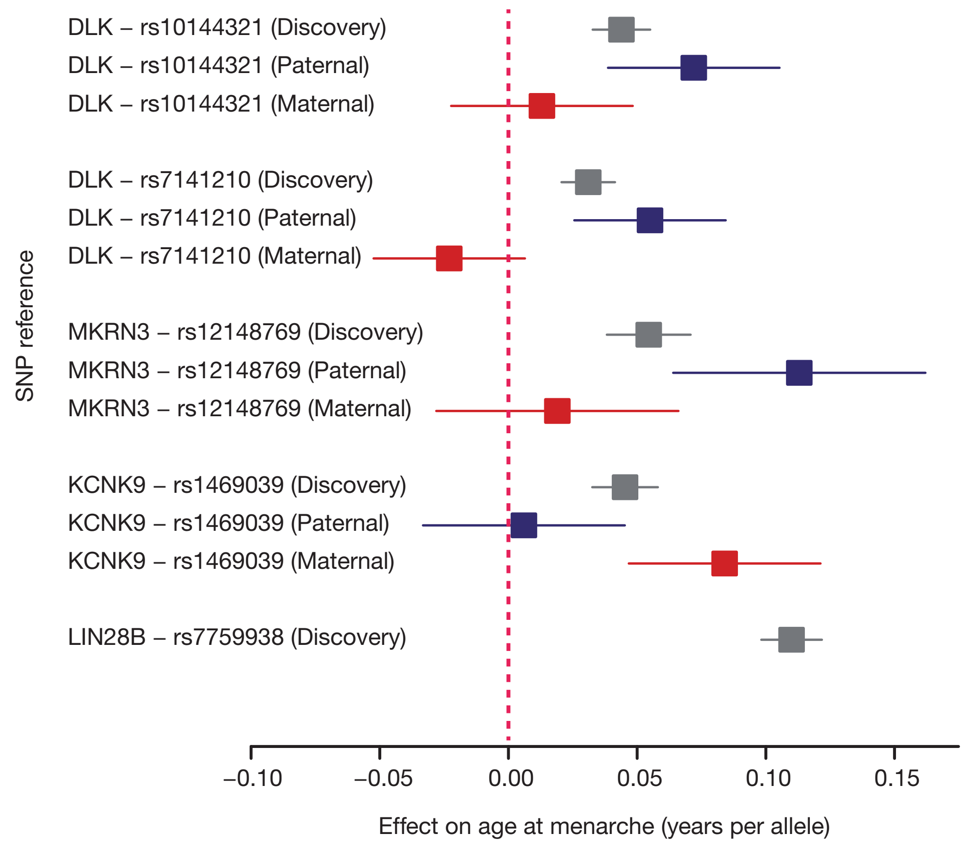


Figure 2 | Forest plot of parent-of-origin-specific allelic associations at three imprinted menarche loci. The forest plot illustrates the associations of variants in four independent genomic signals for age at menarche that are located in three imprinted gene regions. For each variant, squares (and error bars) indicate the estimated per-allele effect sizes on age at menarche in years (and 95% confidence intervals) from the standard additive models in the combined ReproGen meta-analysis (grey), and separately for the paternally inherited (blue) or maternally inherited allele (red) in up to 35,377 women from the deCODE study. The association for the menarche locus with the largest effect size at *LIN28B* is also shown for reference, illustrating the similar magnitude of effect size at the *MKRN3* locus when parent-of-origin is taken into account.

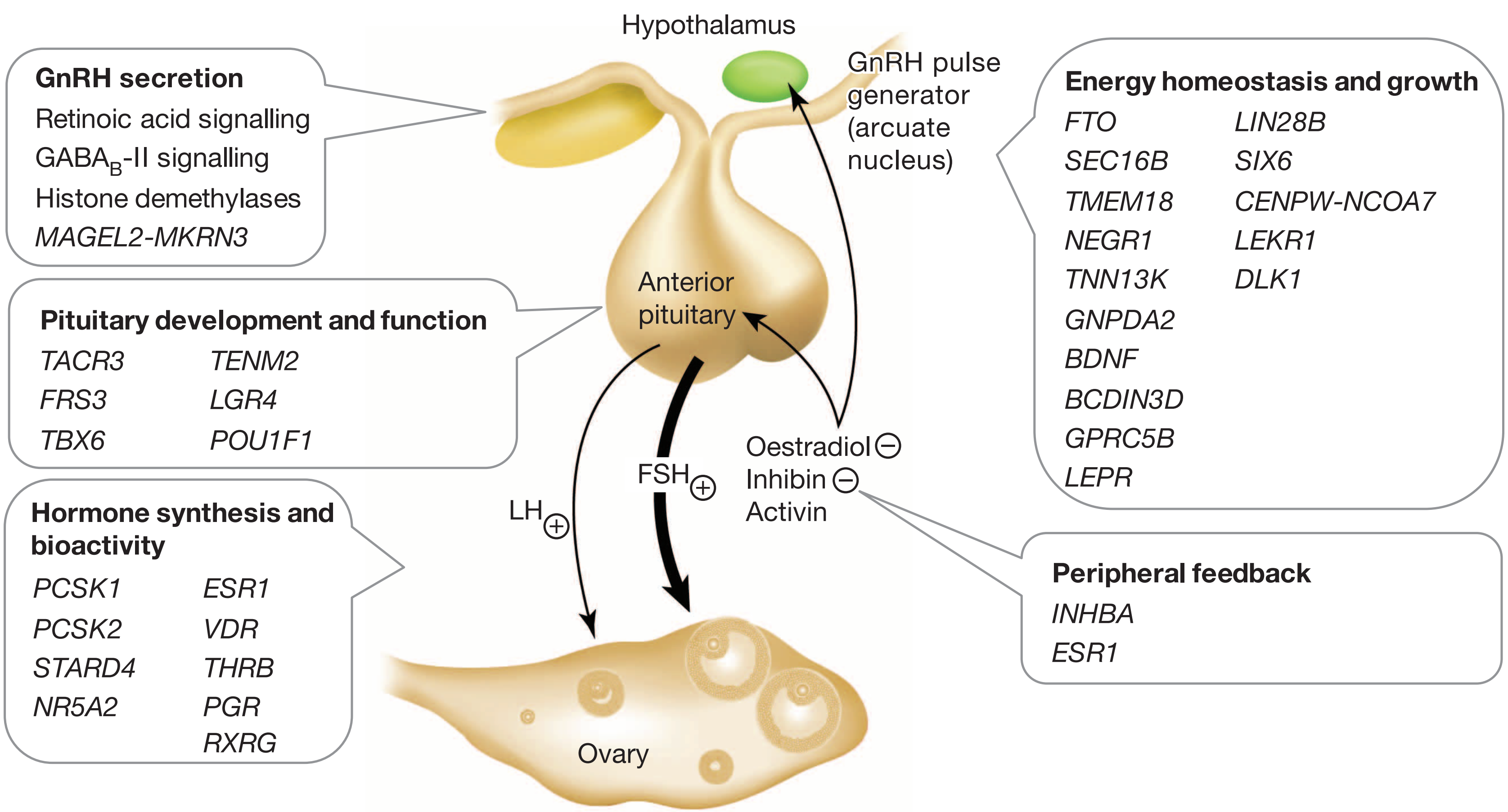
2014 AAVV Genetics Menarche

LETTER

doi:10.1038/nature13545

Parent-of-origin-specific allelic associations among 106 genomic loci for age at menarche

A list of authors and their affiliations appears at the end of the paper



2014 AAVV Genetics Menarche

MECHANISMS OF DISEASE

Effect of In Utero and Early-Life Conditions on Adult Health and Disease

Peter D. Gluckman, M.D., D.Sc., Mark A. Hanson, D.Phil., Cyrus Cooper, M.D., and Kent L. Thornburg, Ph.D.

N Engl J Med 2008;359:61-73.

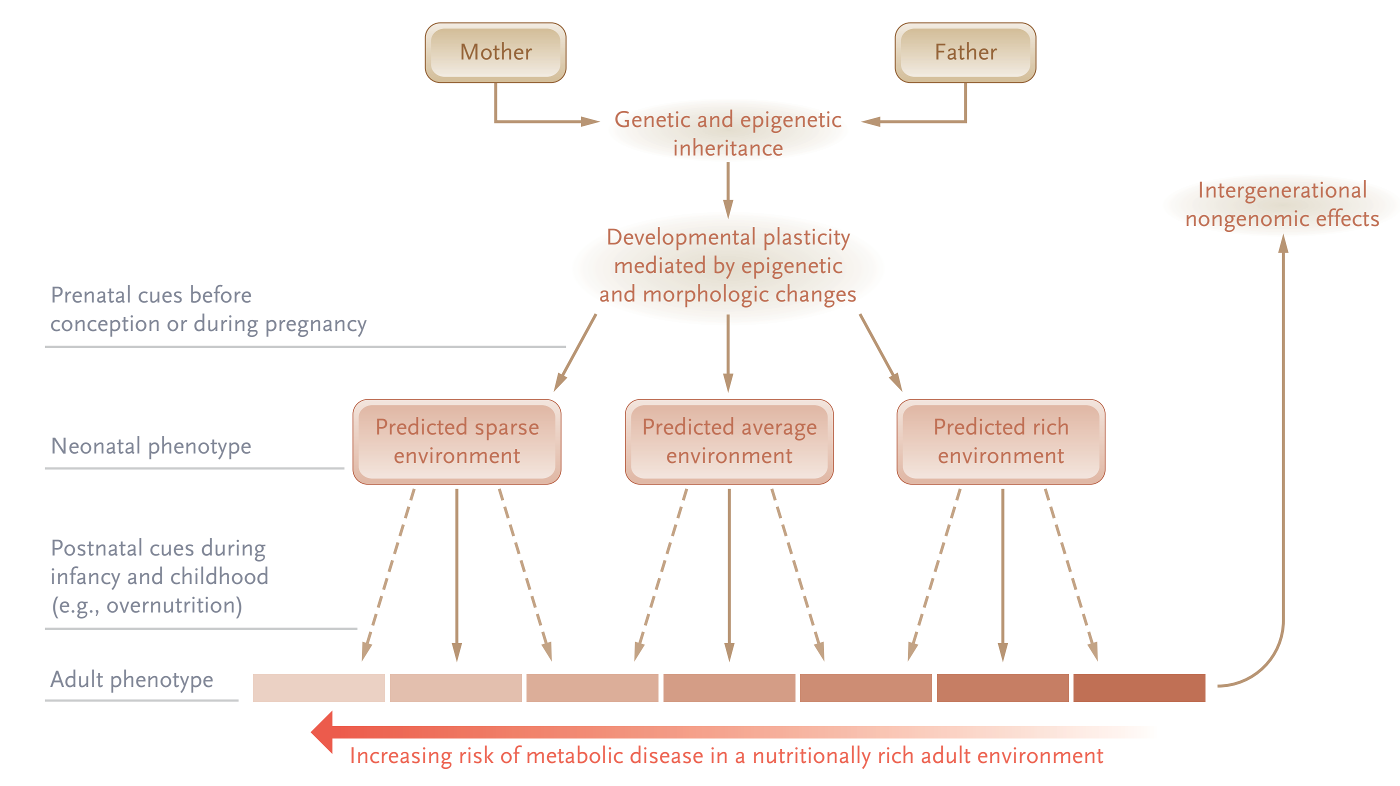
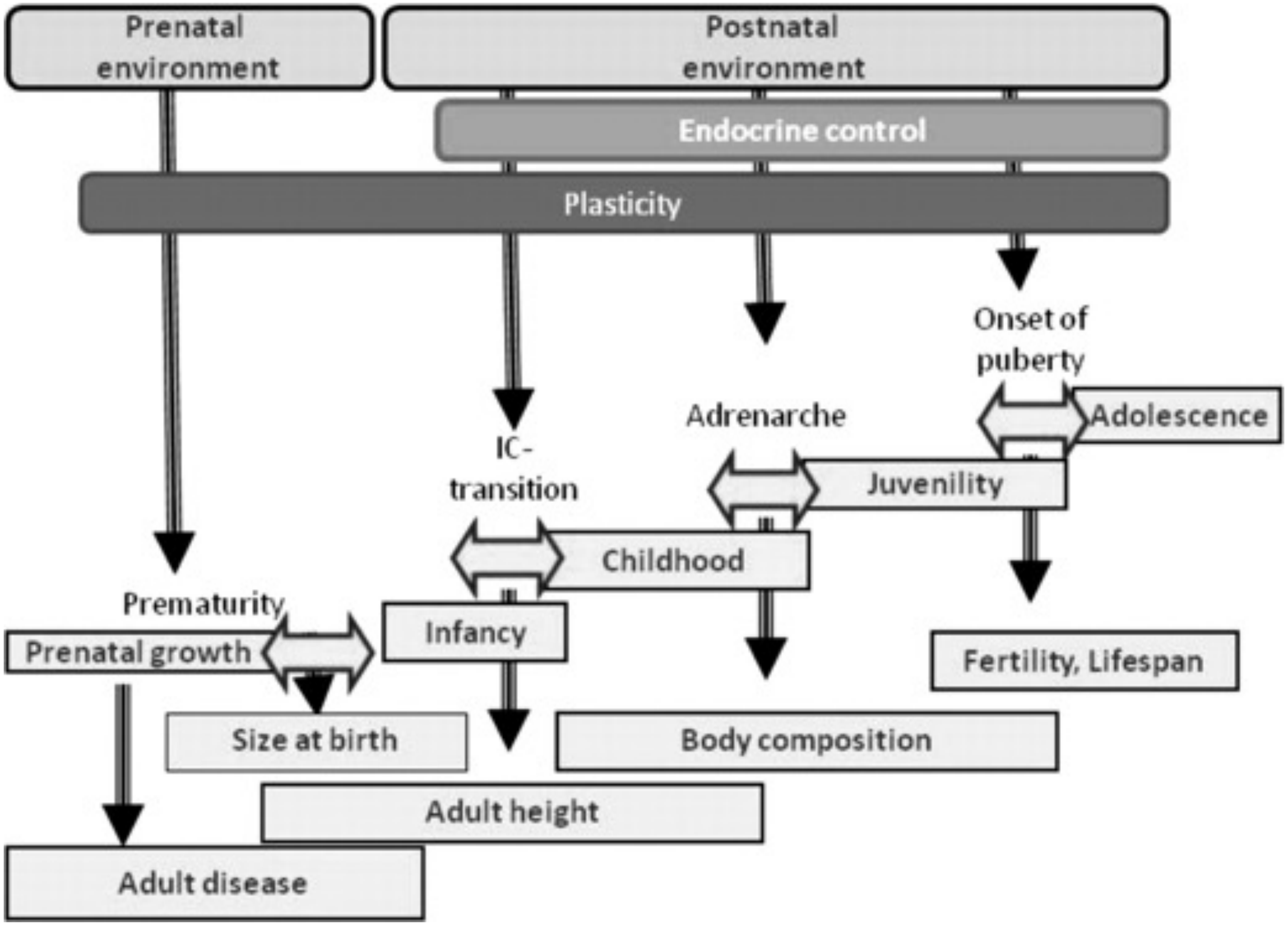


Figure 5. Environmental Cues during Development, Developmental Plasticity, and Determination of the Adult Phenotype.

Prenatal cues predicting a nutritionally sparse environment will cause a shift in the trajectory of structural and functional development toward a phenotype matched to that environment. Such a phenotype will have a reduced capacity to cope with a nutritionally rich environment later in life, increasing the risk of metabolic disease. Postnatal cues, such as childhood overnutrition leading to compensatory growth, could further shift the positioning of the adult phenotype, exacerbating the mismatch (dashed lines) between phenotype and environment. Although there is a continuous range of possible developmental trajectories and multiple sequential cues that act during development, for simplicity only two developmental cues (before and after birth) and three trajectories are shown.

FIG. 1.

Preadult periods of adaptive plasticity in the transition between life-history phases



Hochberg, Z. et al. Endocr Rev 2011;32:159-224

ENDOCRINE REVIEWS

Frontiers in Neuroendocrinology xxx (2014) xxx–xxx

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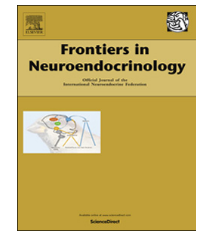
journal homepage: www.elsevier.com/locate/yfrne



Review

Epigenetic regulation of female puberty

Alejandro Lomniczi *, Hollis Wright, Sergio R. Ojeda *

Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University, 505 NW 185th Ave, Beaverton, OR 97006, USA

2014 Lomniczi Epigenetics Puberty

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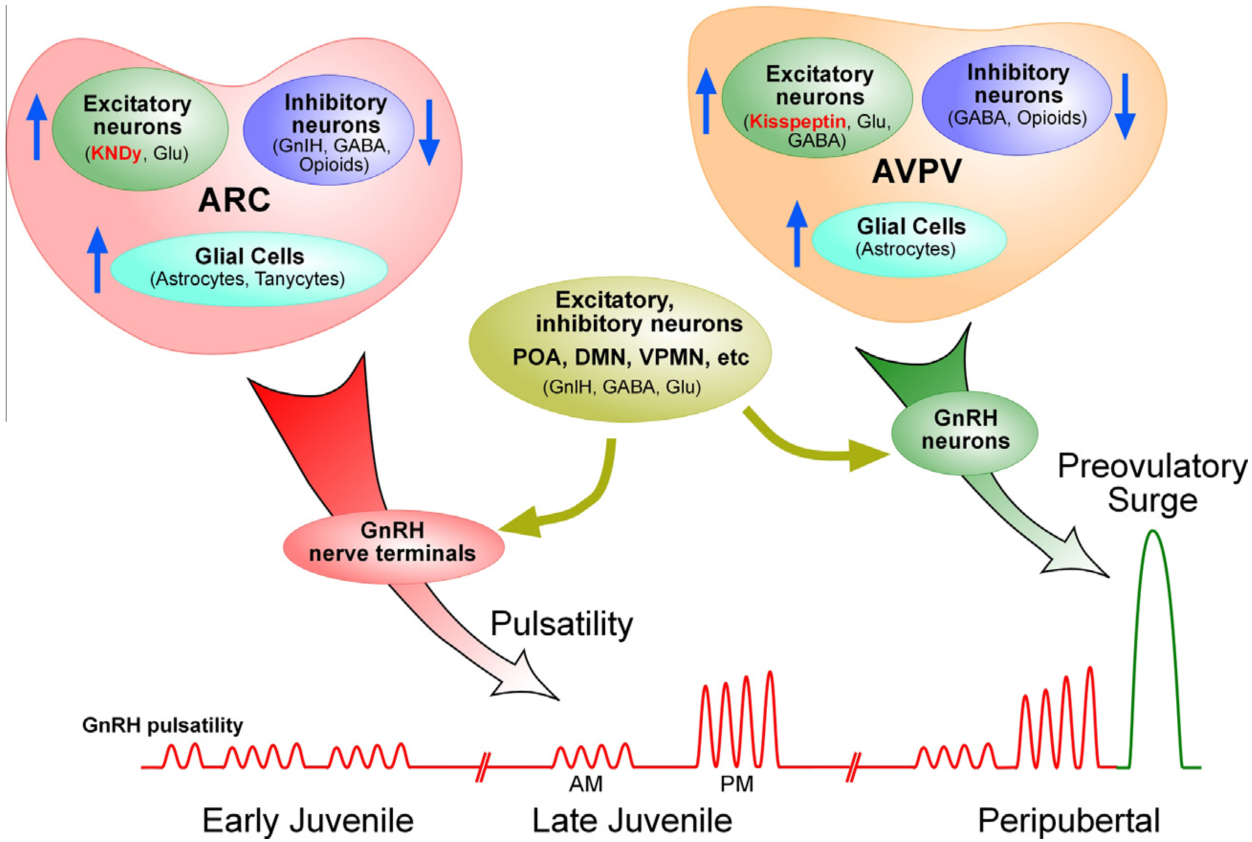

Fig. 1. *The hypothalamic control of pulsatile and surge LH release*. The hypothalamic control of puberty involves excitatory and inhibitory transsynaptic inputs to GnRH neurons, in addition to facilitatory glia-to-neuron signaling. According to this concept, the initiation of puberty involves a shift from a predominantly inhibitory (shown by downward arrows) to an excitatory mode of control (upward arrows). This shift results in diurnal activation of pulsatile GnRH release, which leads to increased LH pulsatility, the first endocrine manifestation of puberty. The change in pulsatile GnRH release results from activation of excitatory networks (neuronal and glial) operating in the ARC of the hypothalamus, with KNDy neurons playing a central role. The neuronal and glial systems involved appear to predominantly target GnRH nerve terminals at the median eminence. The preovulatory surge of gonadotropins is a later event at puberty and is triggered by activation of AVPV kisspeptin neurons responding to an elevation in circulating estrogen levels. The potential involvement of other excitatory neurons, such as those that use glutamate (Glu) and GABA acting via $GABA_A$ receptors for neurotransmission, is also indicated. However not all the excitatory or inhibitory systems regulating pulsatile GnRH release are located in the ARC or AVPV. Additional inhibitory neurons, such as those releasing GnIH are located in the dorsomedial nucleus (DMN), and groups of excitatory/inhibitory neurons are located in the medial preoptic area (POA), medial amygdala and ventral premammillary nucleus (VPMN).

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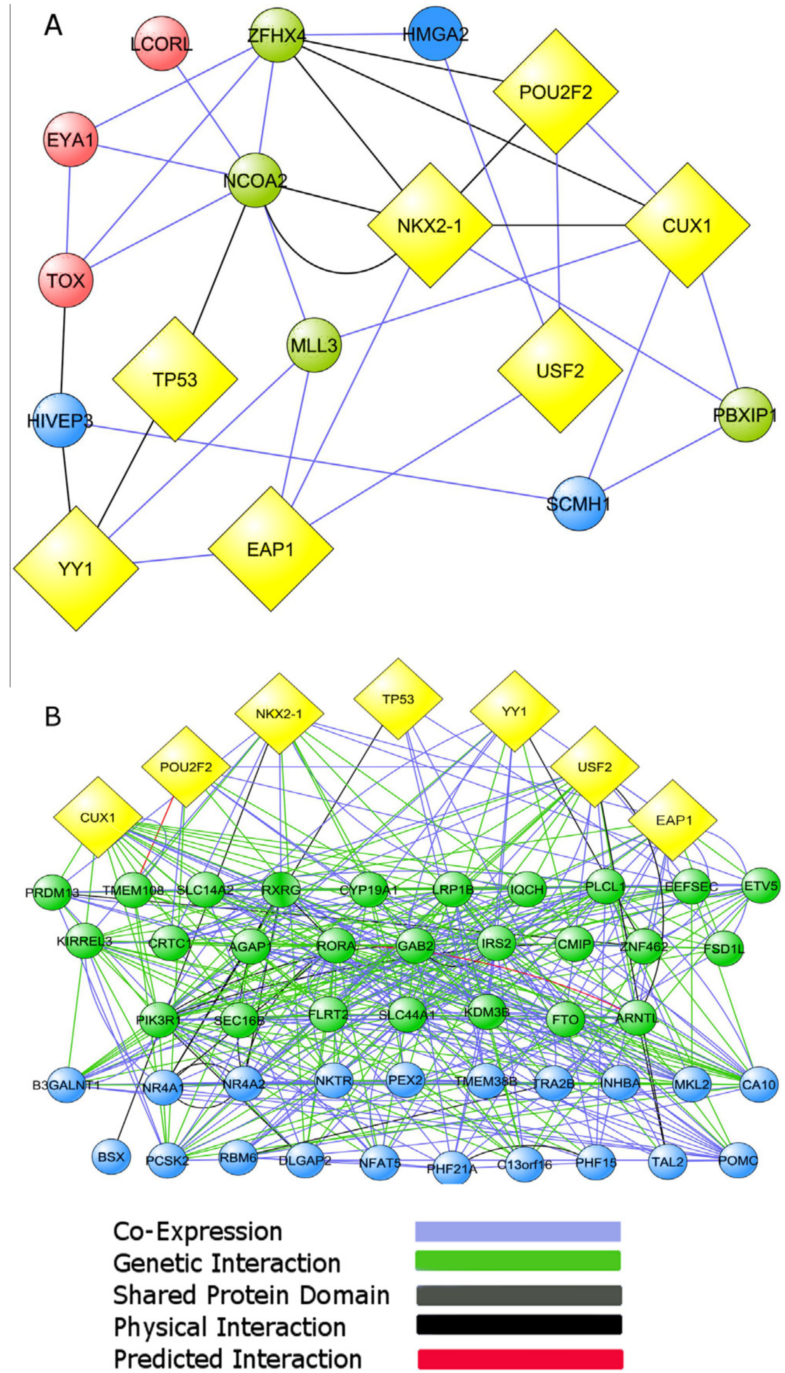

Fig. 2. *Network connectivity of the most interconnected bovine puberty genes and human menarche-related genes to the central nodes of a TRG network derived from rats and nonhuman primates.* (A) The ten most connected genes of a bovine puberty gene network (Fortes et al., 2011) are first neighbors of the TRG central nodes (depicted as yellow diamonds). (B) Genes identified by GWAS as associated to the age of human menarche (Ong et al., 2009; Perry et al., 2009; Sulem et al., 2009; He et al., 2009; Elks et al., 2010; Cousminer et al., 2013; Tanikawa et al., 2013) are also highly connected to both the five original TRG central nodes (Roth et al., 2007 and to the upper-echelon transcriptional regulators *TTF1/NKX2.1* and *EAP1/IRF2BPL* (yellow diamonds). Bovine puberty genes and menarche-related genes connected to multiple TRGs are depicted as green circles. Genes connected to at least one TRGs are shown as blue circles. Genes not connected to any TRG are represented as red circles. In both cases the connectivity is via co-expression (blue), predicted interaction (red), shared protein domain (gray), physical interactions (black), and genetic interaction (green) indicated by the GeneMANIA network construction algorithm. The thickness of each line indicates the strength of the evidence supporting that type of interaction in the Gene MANIA database. The distribution of nodes in B does not reflect a hierarchical distribution; instead it intends to emphasize the different degrees of connectivity that exists between central TRGs and menarche-related genes.

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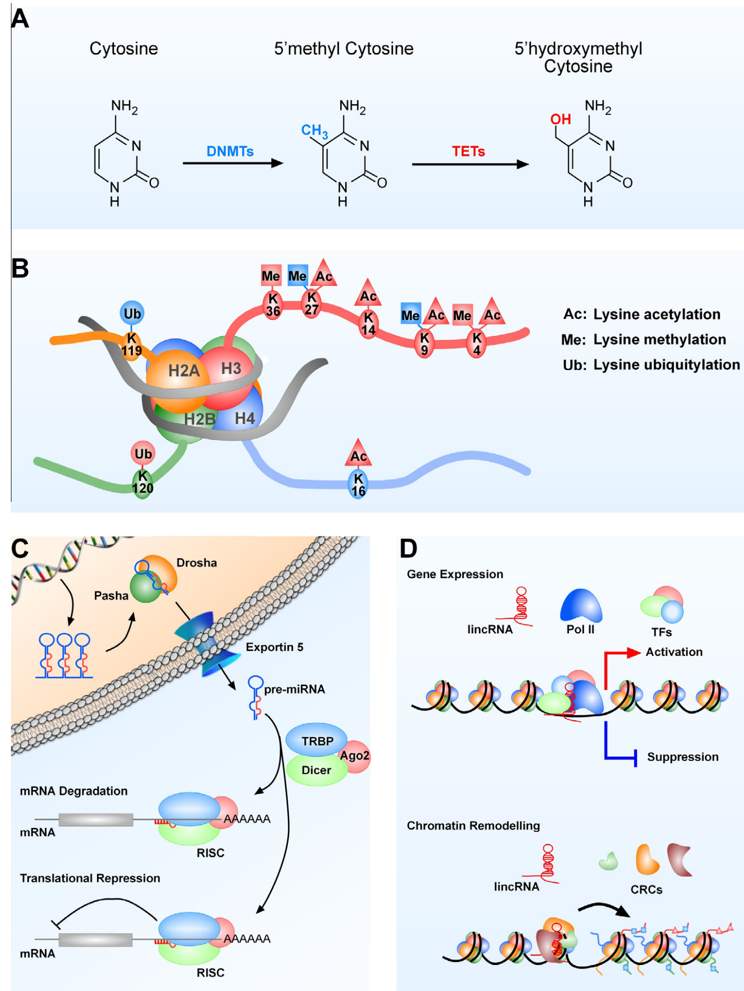

Fig. 3. *Modes of epigenetic regulation.* (A) DNA methylation. Methylation of cytosine at position 5 is carried out by DNMTs (DNMT1, DNMT3a and DNMT3b), and inactivation of this methyl group by hydroxymethylation is carried out by the TET enzymes. Names in blue color indicate repression and red color indicates activation of gene expression. (B) Histone PTMs. Only the PTMs catalyzed by the PcG and TrxG complexes (methylation, ubiquitination) or associated (acetylation) with TrxG-dependent PTMs are shown. Histone PTM in blue = PTM associated with gene repression; histone PTM in red = PTM associated with gene activation. (C) miRNAs. The pathway leading to miRNA production is outlined and the fact that miRNAs silence mRNA expression by inducing either mRNA degradation or translational repression is emphasized. (D) Long intergenic noncoding RNAs. Two mechanisms of lincRNA action are depicted. In one of them, lincRNAs modify gene expression by serving as landing pads for transcription factors that either repress or activate transcription. The other mechanism consists of lincRNAs directing the organization of chromatin states to specific genomic regions involved in gene regulation. DNMTs = DNA methyltransferases, TETs = ten eleven translocation (dioxygenase) enzymes; H = histone; Pasha = nuclear protein that is part of the microprocessor complex required for miRNA processing. Pasha associates with the RNA III enzyme Drosha. Drosha = RNA III enzyme that cleaves pri-miRNA (the primary transcript of miRNAs) to precursor (pre)-miRNA, which contains a stem-loop structure; Dicer = endoribonuclease that cleaves pre-miRNA into 20–25 mer double-stranded miRNAs; TRBP = human immunodeficiency virus transactivating response RNA-binding protein; it recruits Dicer to Ago2 for miRNA processing; Ago2 = Argonaut 2, the catalytic component of RISC; RISC = RNA induced silencing complex; Pol II = RNA polymerase 2; TF = transcription factor; CRC = chromatin remodeling complex.

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Review

Epigenetic regulation of female puberty

Alejandro Lomniczi *, Hollis Wright, Sergio R. Ojeda *

Division of Neuroscience, Oregon National Primate Research Center, Oregon Health & Science University, 505 NW 185th Ave, Beaverton, OR 97006, USA

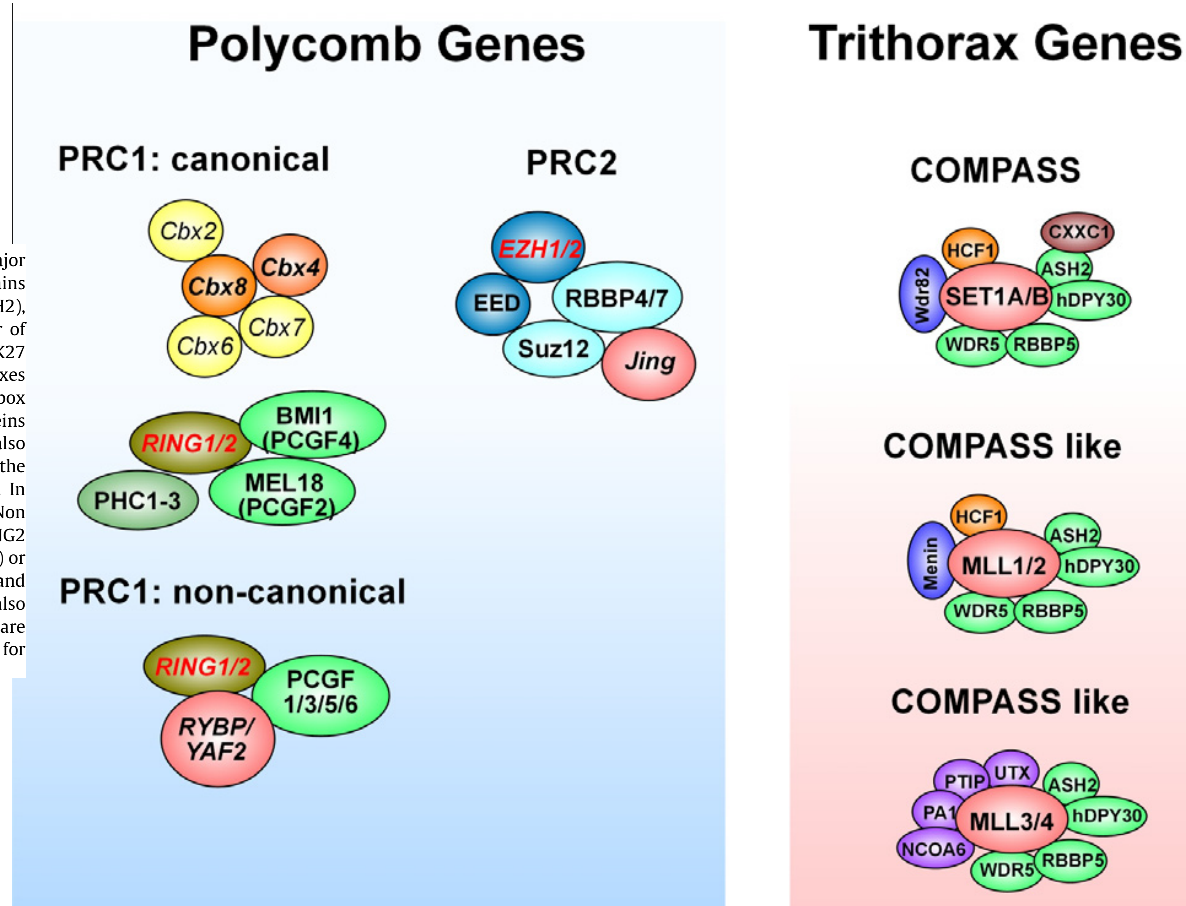

Fig. 4. *Subunit composition of the PcG and COMPASS families*. The three major Polycomb repressive complexes (PRCs) are depicted. The PRC2 complex contains the histone methyltransferase enhancer of zeste homologue 1 (EZH1) or EZH2), which together with embryonic ectoderm development (EED) and suppressor of zeste 12 homolog (SUZ12) catalyzes the trimethylation of histone H3 at lysine K27 (H3K27me3). Multiple forms of the PRC1 complex exist. Canonical PRC1 complexes contain combinations of at least five Pc (Polycomb) proteins (known as chromobox proteins: CBX2, CBX4, CBX6, CBX7 and CBX8), two Psc (posterior sex comb) proteins (BMI1, also known as PCGF4 (polycomb group RING finger protein 4), MEL18 (also known as PCGF2) and one of two RING proteins, RING1 or RING 2 that provide the catalytic core to the complex because they have E3 ubiquitin ligase activity. In addition PRC1 complexes contain three polyhomeotic-like proteins (PHC1-3). Non canonical PRC1 complexes lack CBX proteins and contain instead a RING1 or RING2 protein that forms a complex with either RYBP (RING1 and YY1 binding protein) or YAF2 (YY1-associated factor) and one of four PCGF proteins different from BMI1 and MEL18 (PCGF1, 3, 5 or 6). The six known mammalian COMPASS complexes are also shown. Although all of them methylate H3K4 at lysine 4, different complexes are responsible for the mono, di or tri methylation of this amino acid (see text for details). Modified from Mohan et al. (2012).

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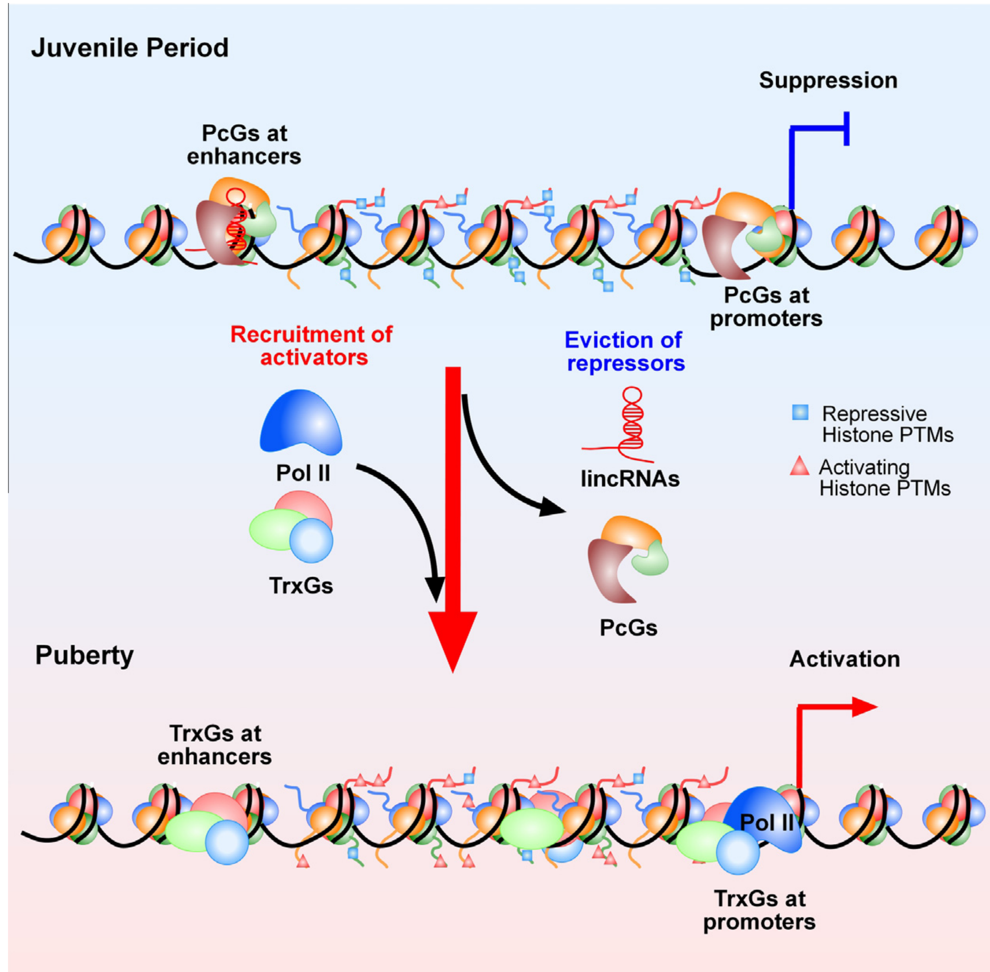

Fig. 5. *Postulated epigenetic mechanisms controlling the onset of female puberty*. This model predicts the existence of an antagonistic (Yin-Yang) mechanism of transcriptional regulation underlying the developmental changes in expression of genes that facilitate pubertal development. According to this concept, the transcriptional activity of these genes (*Kiss1*, *Tac2, Nell2, TTF1*, others) is repressed during prepubertal development by silencing molecules, such as the PcG complex. PcG proteins catalyze the formation of a repressive chromatin structure characterized by an abundance of histone PTMs associated with gene silencing (such as H3K27me3). As puberty approaches, these "writers" of a repressive chromatin configuration are evicted from, and the content of histone repressive marks is reduced at, promoter regions controlling puberty-activating genes. Along with this change, writers of histone PTMs associated with transcriptional activation, such as H3K4me3 and H3K9,14ac, are recruited to these regulatory regions resulting in enhanced gene expression. A strong candidate for this activational role is the TrxG activating complex, which antagonizes the silencing effect of PcG by both catalyzing the methylation of histone 3 at lysine 4 (H3K4me3, an activating histone mark) and binding to promoter DNA containing this mark. It is also envisioned that a similar relationship operates in distal enhancers regions controlling puberty-related genes. In this case, PcG deposition of the histone repressive mark H3K27me3, coupled to the presence of H3K4me1 and the absence of Pol II, define the presence of a latent enhancer. This inactive enhancer acquires an active configuration following the implementation of H3K27ac by the TrxG complex, and the recruitment of Pol II in the presence of H3K4me1 (also catalyzed by TrxG).

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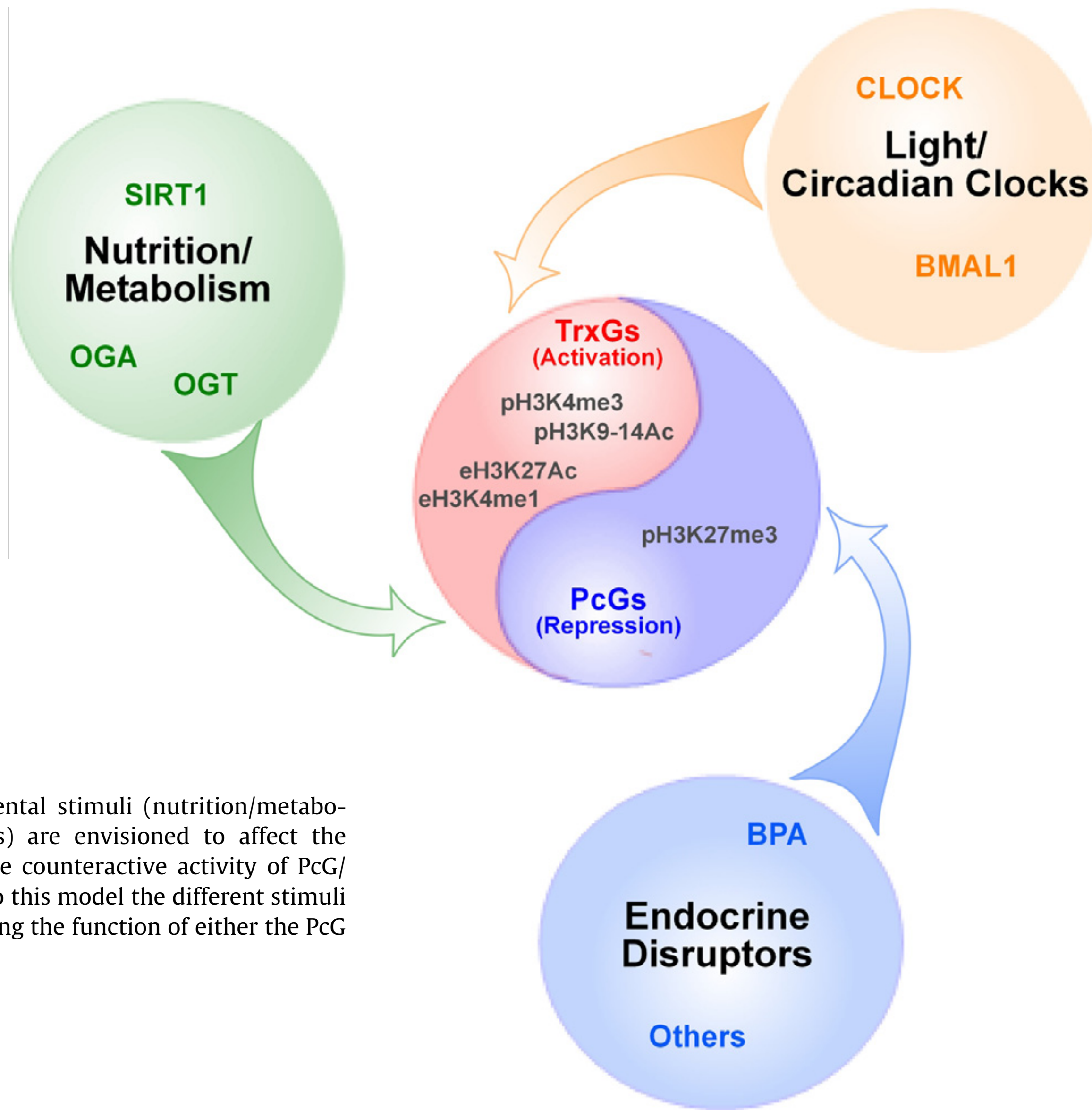

Fig. 6. Different external and internal environmental stimuli (nutrition/metabolism, light/circadian clocks, endocrine disruptors) are envisioned to affect the timing and progression of puberty by altering the counteractive activity of PcG/TrxG-mediated epigenetic machinery. According to this model the different stimuli depicted can affect the time of puberty by modifying the function of either the PcG or TrxG complex or both.

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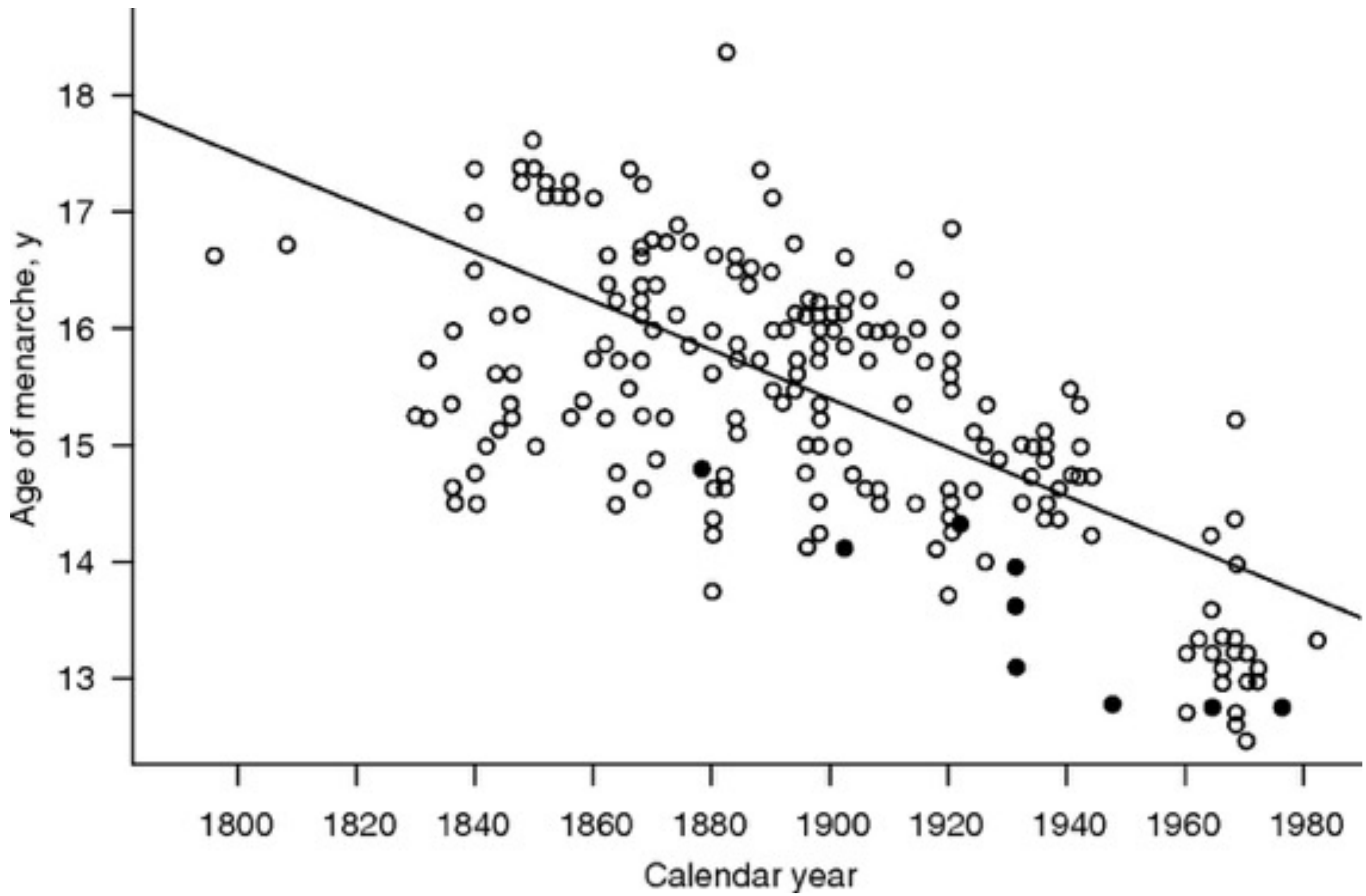
Role of Environmental Factors in the Timing of Puberty

Susan Y. Euling, Sherry G. Selevan, Ora Hirsch Pescovitz and Niels E. Skakkebaek

Pediatrics 2008;121;S167-S171
DOI: 10.1542/peds.2007-1813C

Mean or median age of menarche in Europe and the United States as a function of calendar year from 1790 to 1980



Euling, S. Y. et al. Pediatrics 2008;121:S167-S171

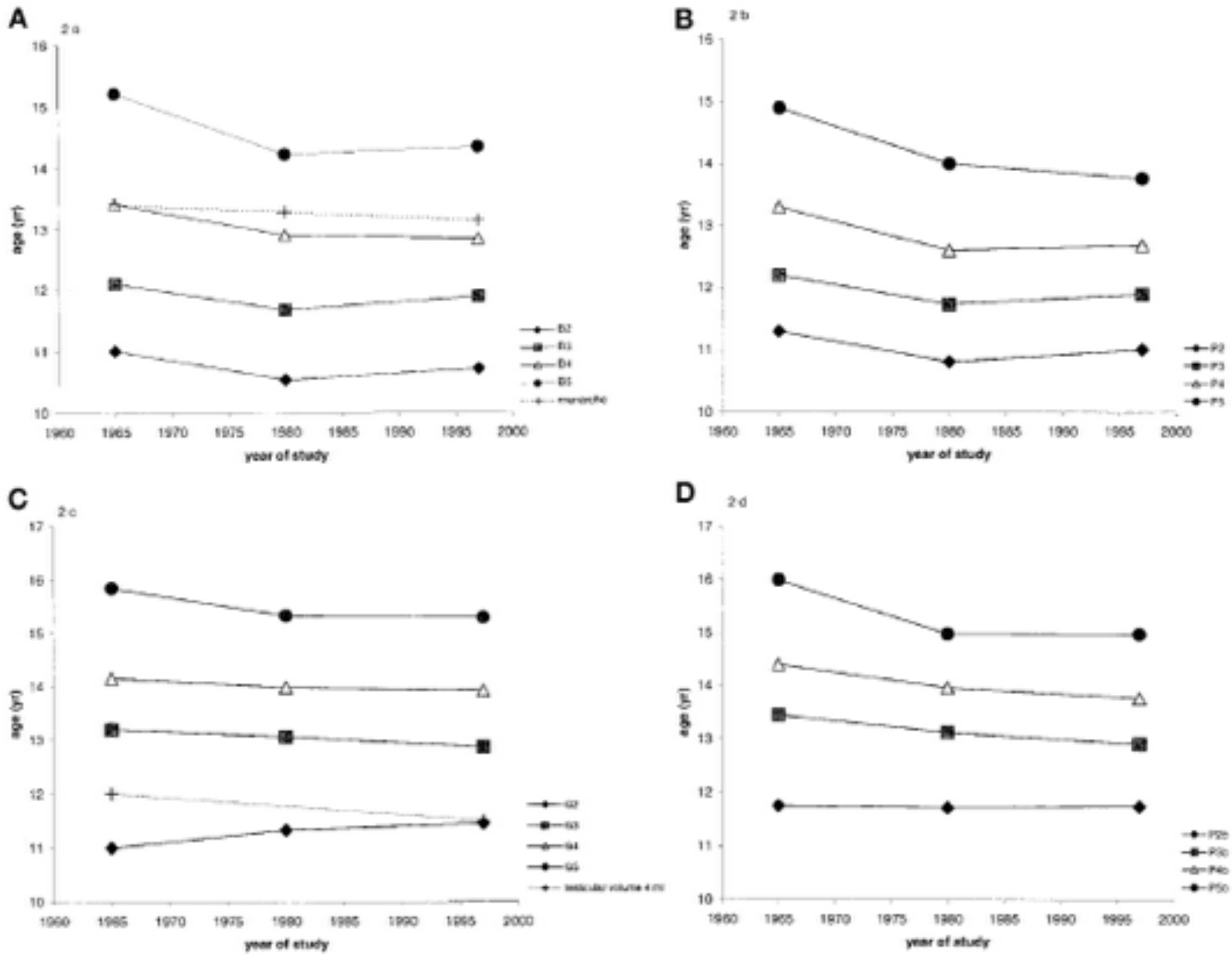


Figure 2. Sexual maturation in The Netherlands 1965–1997 [(1, 11) and this study]; the P_{50} values of the different pubertal stages are given. *A*, breast stage and menarche; *B*, pubic hair stage in girls; *C*, genital stage in boys and testicular volume 4 mL; *D*, pubic hair stage in boys.

Mul D et Al. Pediatr Res 2001

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Recent Decline in Age at Breast Development: The Copenhagen Puberty Study
Lise Aksglaede, Kaspar Sørensen, Jørgen H. Petersen, Niels E. Skakkebæk and Anders Juul
Pediatrics 2009;123;e932-e939
DOI: 10.1542/peds.2008-2491

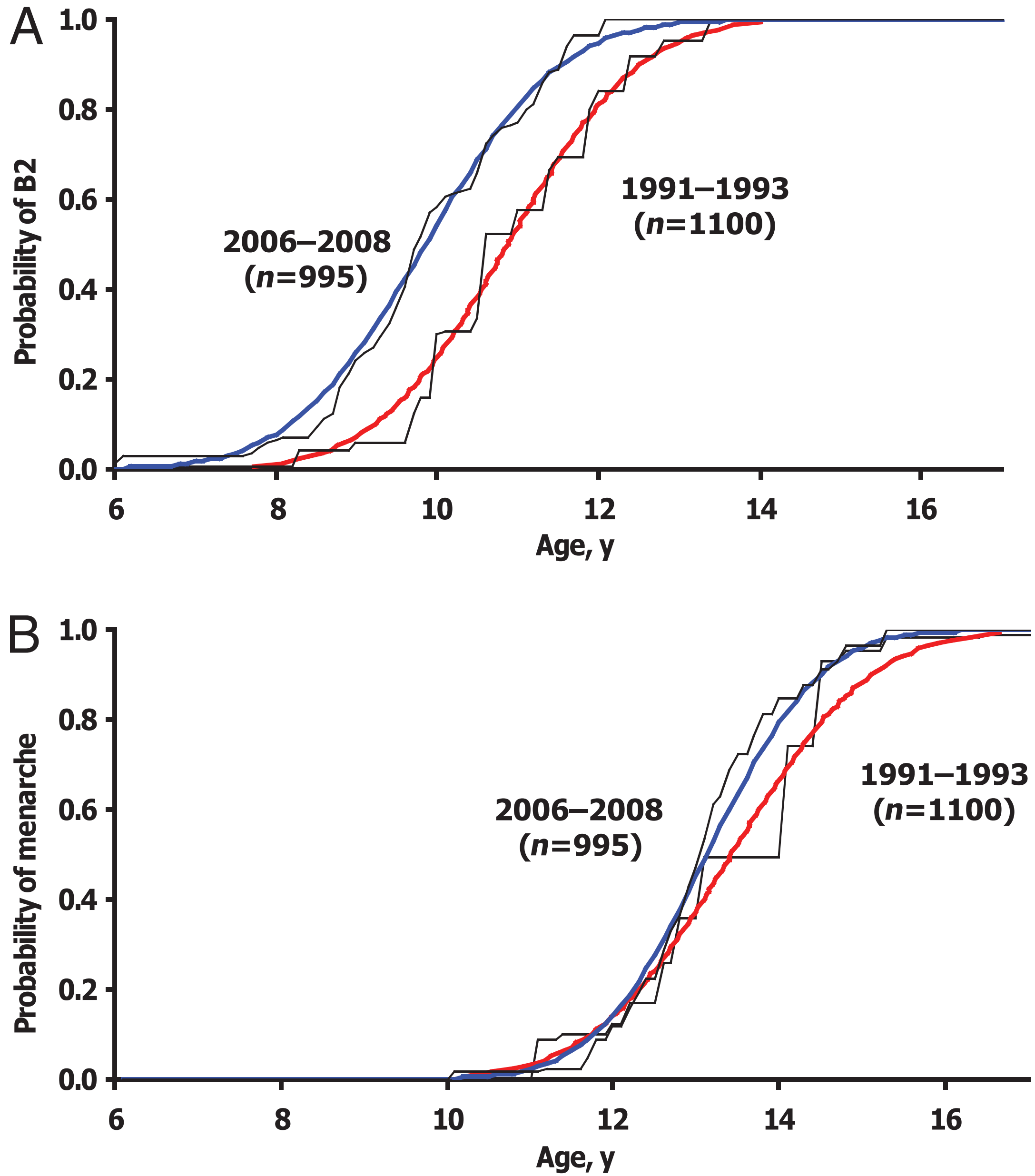
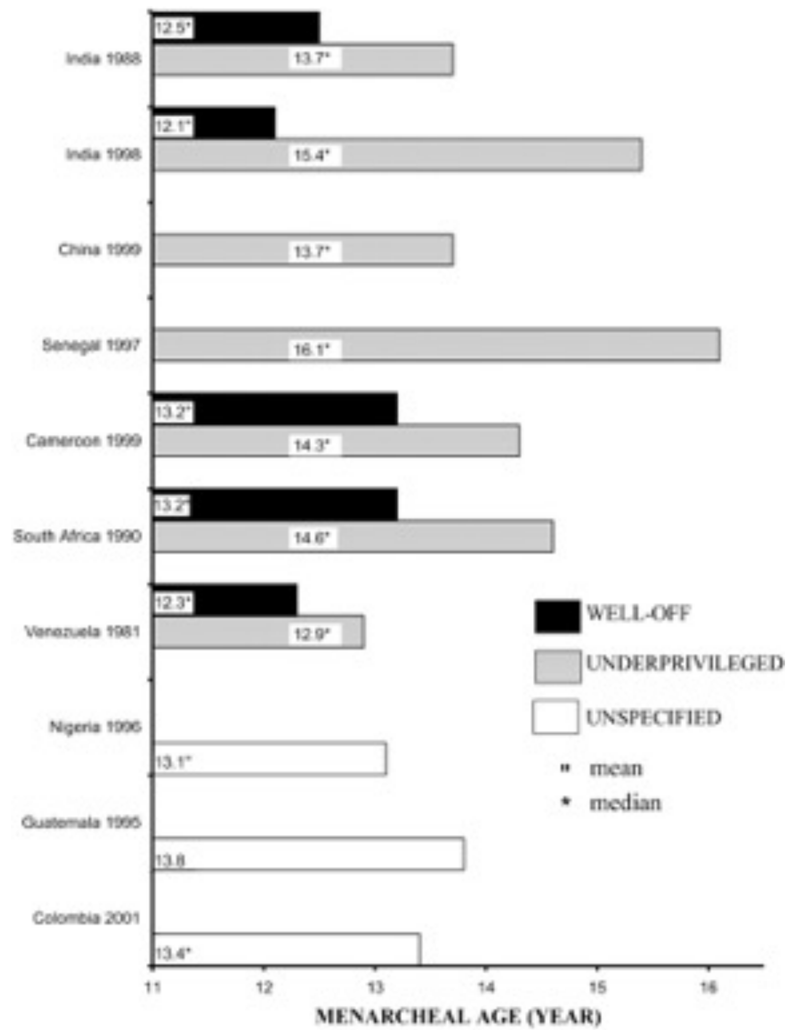
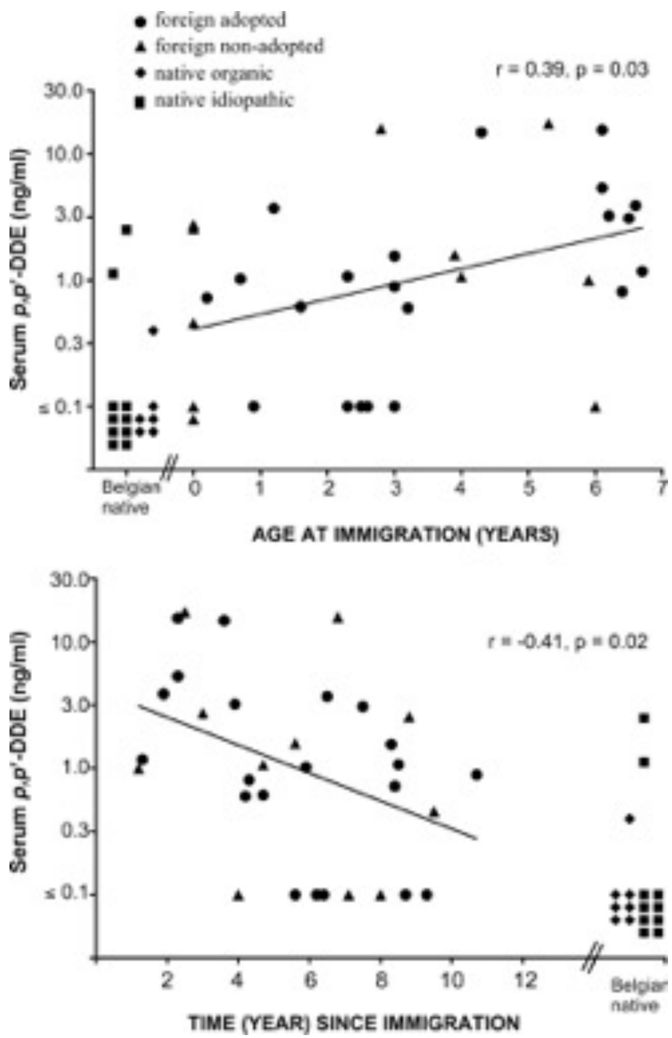


FIG. 3. Average (mean or median) menarcheal age in different developing countries



Parent, A.-S. et al. Endocr Rev 2003;24:668-693

FIG. 7. Serum levels of p,p'-DDE, a derivative of the organochlorine pesticide DDT in different patients with sexual precocity



Parent, A.-S. et al. Endocr Rev 2003;24:668-693

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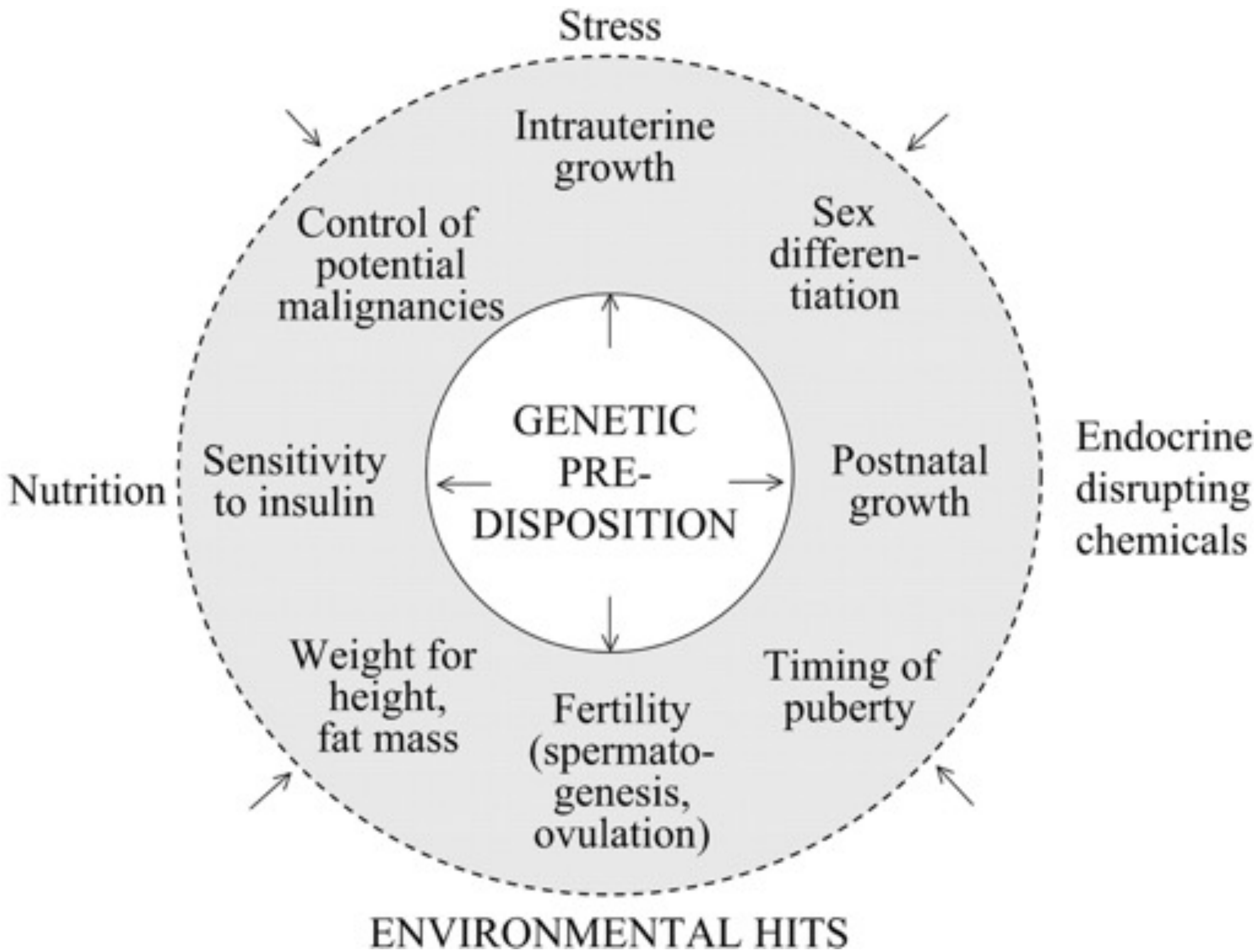
FIG. 8. Integration of timing of puberty within a spectrum of processes that are influenced by both genetic and environmental factors



Parent, A.-S. et al. Endocr Rev 2003;24:668-693

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Public Health Implications of Altered Puberty Timing

Mari S. Golub, Gwen W. Collman, Paul M.D. Foster, Carole A. Kimmel, Ewa Rajpert-De Meyts, Edward O. Reiter, Richard M. Sharpe, Niels E. Skakkebaek and Jorma Toppari

Pediatrics 2008;121;S218-S230

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TABLE 1 Large-Scale Studies of Pubertal Timing and Adolescent Risk Behaviors

Reference	Region/Study/Sample	Outcomes	Puberty Measure	Finding
Kaltiala-Heino et al[57–59] (2003, 2001, 2003)	Finland/School Health Promotion Study/*N* = 36 000 14- to 16-y-olds	Depression, anxiety, psychosomatic symptoms, bulimia, drunkenness, drug use, smoking, truancy	Age at menarche, oigarche[a] (<10, 11, 12, 13, and 14 y)	Increased incidence of all problems with decreasing age at puberty in both genders
Williams and Dunlop[144] (1999)	Britain/*N* = 99 14-y-old boys	Questionnaire on conduct problems, norm violations, and illegal acts	Pubertal Development Scale (growth spurt, body hair, skin change, facial hair, voice change)	More delinquency in early or late maturers
Wichstrom[71] (2000)	Norway/Young in Norway Study/ *N* = 9679 12- to 20-y-olds	Suicide, suicide attempts	Self-perception of pubertal timing (earlier or later than peers)	Increased incidence of suicide behavior with early maturation in girls, late maturation in boys

Mari S. Golub, et al. *Pediatrics* 2008;121;S218-S230

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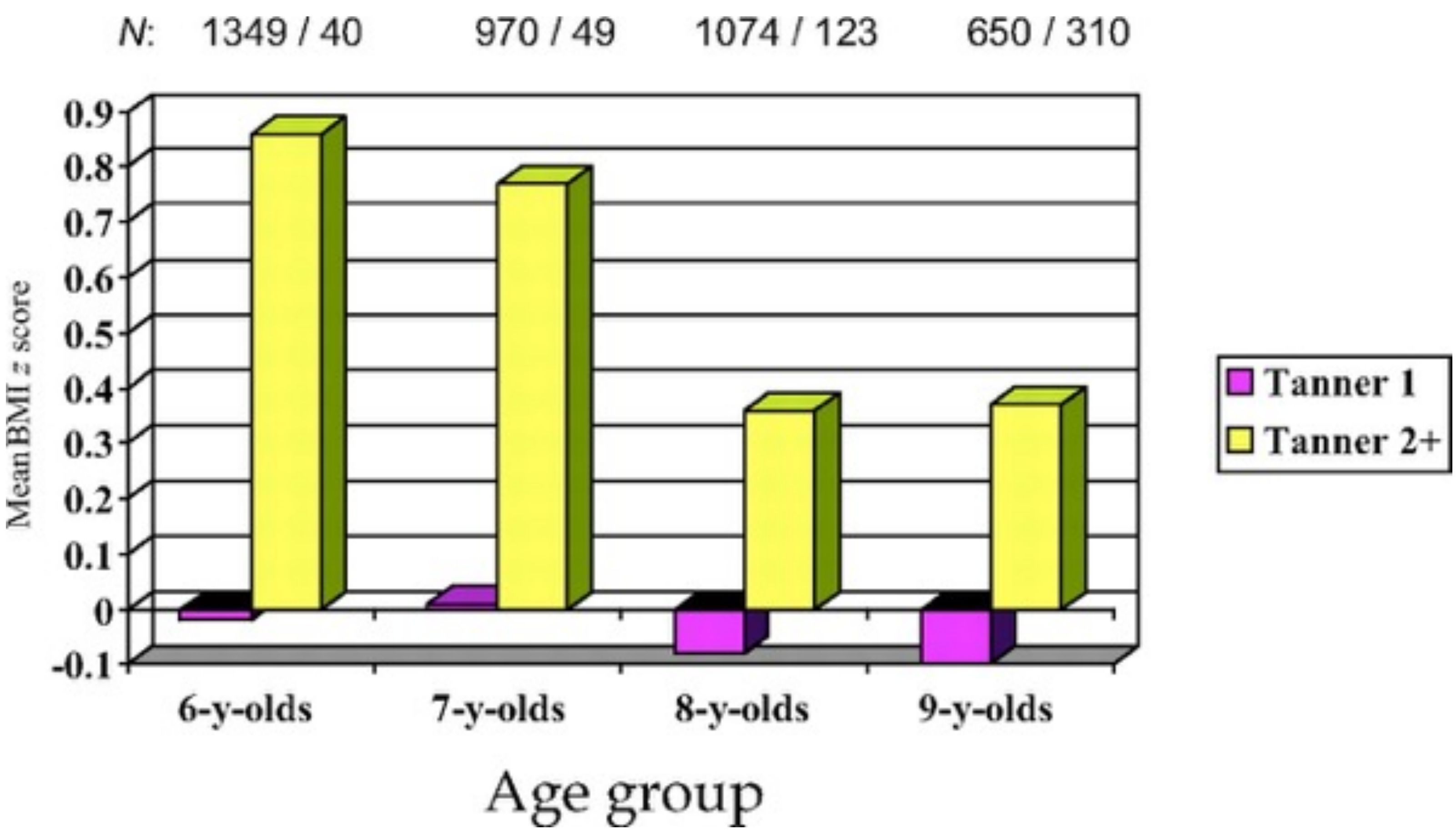
Link Between Body Fat and the Timing of Puberty

Paul B. Kaplowitz

Pediatrics 2008;121;S208-S217
DOI: 10.1542/peds.2007-1813F

FIGURE 1 Mean BMI z scores in 6- to 9-year-old white girls with and without breast development, based on the PROS study data reported by Kaplowitz et al



Kaplowitz, P. B. Pediatrics 2008;121:S208-S217

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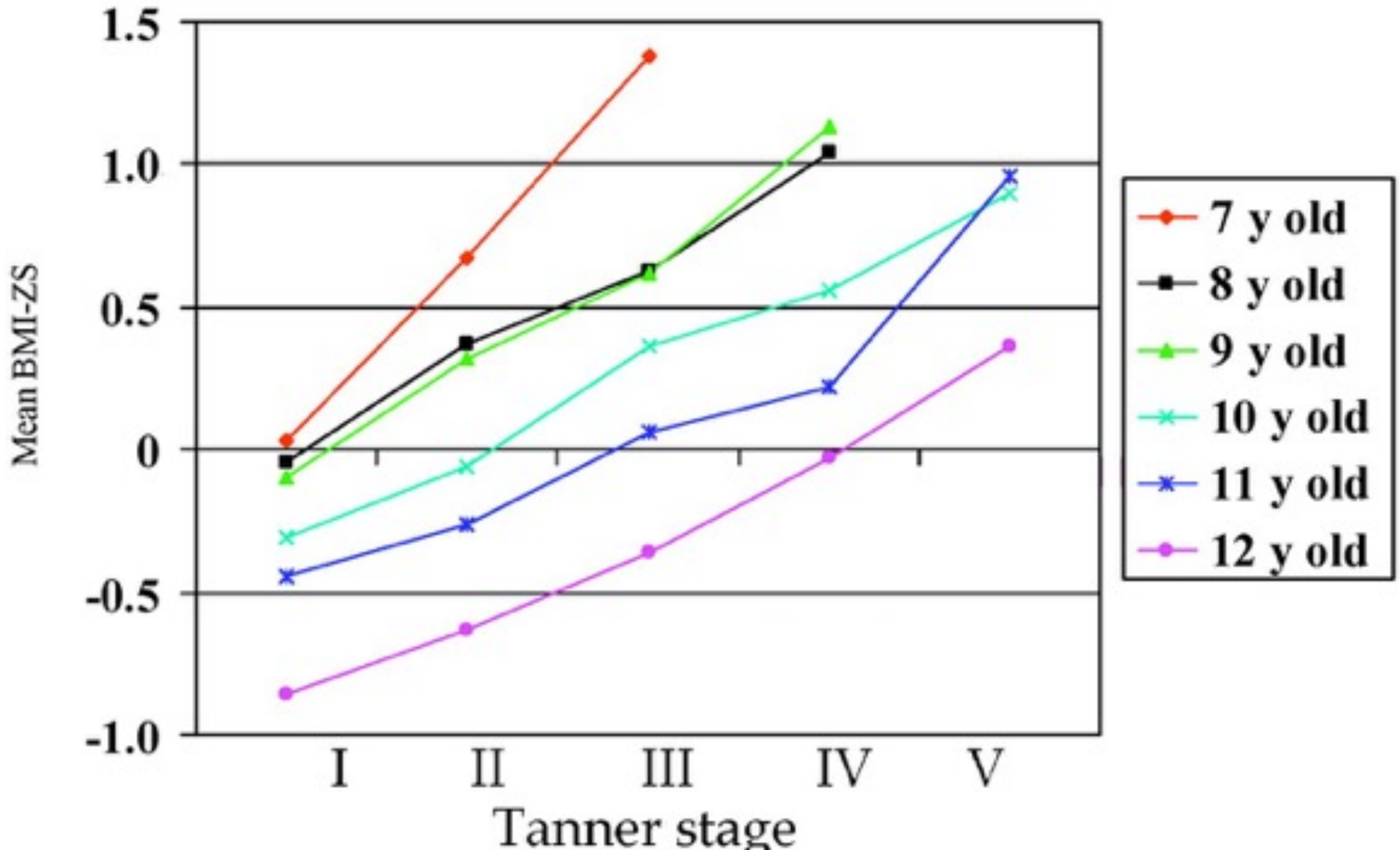
FIGURE 2 The relationship between mean BMI z scores and Tanner staging of breast development in 7- to 12-year-old girls, based on the PROS study data reported by Kaplowitz et al



Kaplowitz, P. B. Pediatrics 2008;121:S208-S217

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Role of Environmental Factors in the Timing of Puberty

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Pediatrics 2008;121;S167-S171
DOI: 10.1542/peds.2007-1813C

"human and animal studies suggest that
endocrine-disrupting chemicals,
particularly the estrogen mimics and antiandrogens,
and body fat
are important factors associated
in altered puberty timing"

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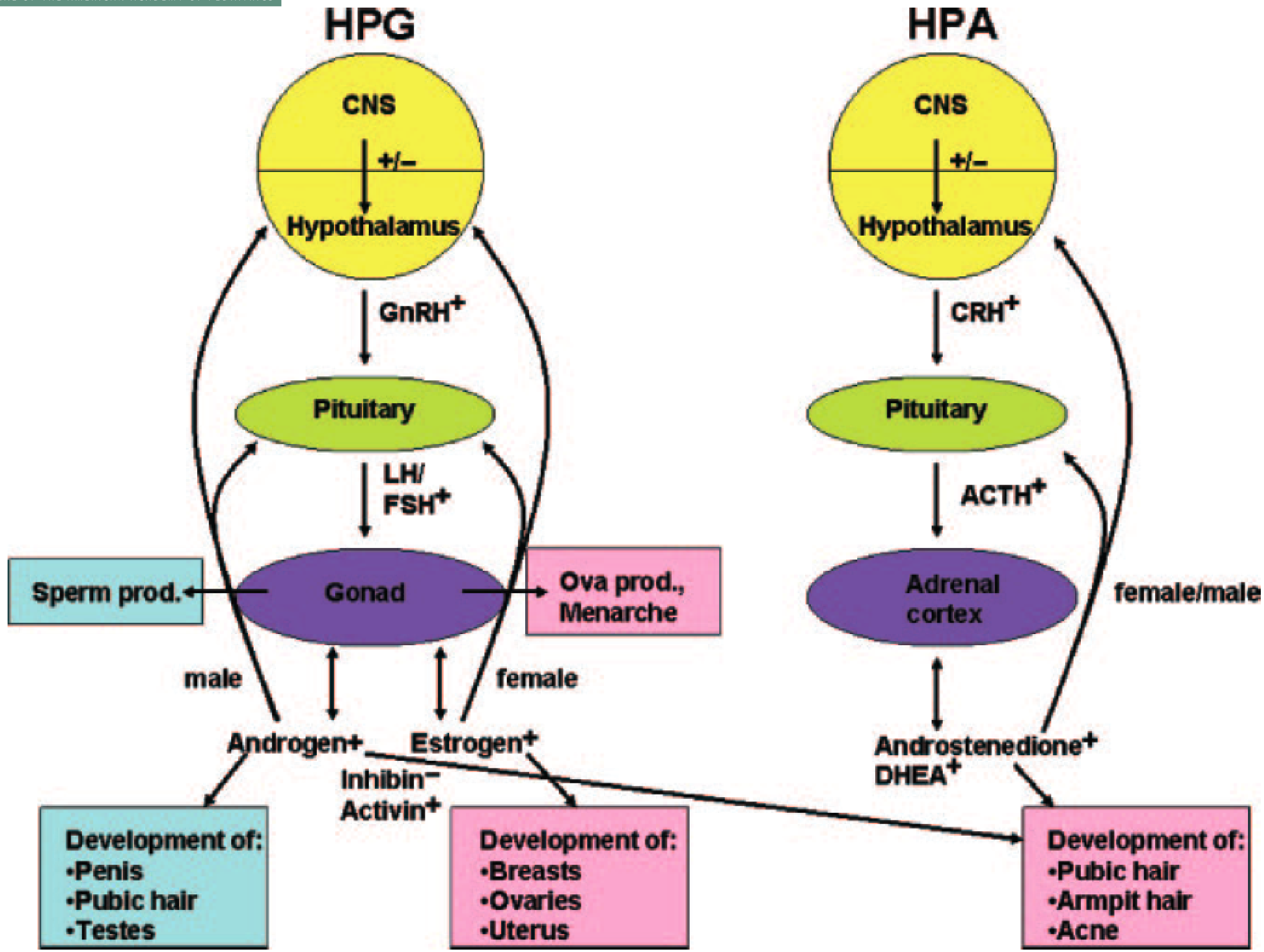

Germaine M. Buck Louis, et al. *Pediatrics* 2008;121;S192-S207

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TABLE 2 Human Studies That Assessed Associations Between Environmental Chemical Exposures and Puberty Timing

Chemical Exposure (Biospecimen)	Population (Sample Size)	Study Design	Findings	Reference
Brominated flame retardant (estimated maternal serum PBB at conception)	US, Michigan girls aged 5–24, accidental in utero and/or lactational exposure (327)	CS/C; assessment of Tanner stages in female offspring; recalled age at menarche in postmenarchal offspring	Earlier menarche and pubic hair development among girls highly exposed in utero and breastfed; no association with breast development	Blanck et al[95] (2000)
DDE (maternal blood, cord blood, and placenta averaged; breast milk)	US, North Carolina boys and girls (594)	C; assessed menarche, Tanner stages by annual questionnaire	Boys: no association; girls: suggestion of earlier breast and pubic hair development with high transplacental and with high lactational exposure	Gladen et al[97] (2000)
DDE (serum)	Girls with precocious puberty: foreign-born girls (26); Belgium girls (15)	CS; serum DDE compared between foreign-born and Belgium girls; all had precocious puberty	Foreign-born girls with precocious puberty had significantly higher DDE concentration than native Belgium girls with precocious puberty.	Krstevska-Konstantinova et al[99] (2001)
DDE (estimated maternal serum DDE at conception)	US, Michigan daughters of women who consumed Great Lakes fish (151)	C; recalled age at menarche	Higher DDE associated with earlier menarche.	Vasiliu et al[98] (2004)
DDT/DDE (serum in adulthood)	Chinese female textile workers, newly married (466)	CS; recalled age at menarche	Higher DDT/DDE associated with earlier menarche	Ouyang et al[101] (2005)
DDE (serum)	US/Canada Mohawk Nation, girls 10–17 (138)	CS; menarche (yes/no)	No association	Denham et al[102] (2005)
Dioxin-like activity (serum; CALUX)	17-y-old Belgium boys (78) and girls (120) from polluted and nonpolluted areas	CS; assessment of Tanner stage by examination (boys and girls), testicular volume (boys), recalled age at menarche (girls).	Boys: no association; girls: girls with high exposure were less likely to have reached the highest stage of breast development; no association with pubic hair development or age at menarche.	Den Hond et al[106] (2002)
Dioxin (serum)	Seveso, Italy, women exposed postnatally and prepuberty to dioxin industrial accident (282)	C; recalled age at menarche	No association; suggestion of earlier menarche among girls exposed before the age of 5	Warner et al[108] (2004)
Endosulfan	India, boys aged 10–17 in exposed (117) and unexposed (90) areas	C/CS; Tanner stage by physical examination; serum hormones and endosulfan levels for 70 exposed, 45 unexposed.	Exposed boys were less mature and had lower testosterone and higher LH than unexposed boys	Saiyed et al[111] (2003)
HCB (serum)	US/Canada Mohawk Nation, girls 10–17 (138)	CS; menarche (yes/no)	No association	Denham et al[102] (2005)
Lead (serum)	US 8- to 16-y-old girls NHANES III (2186)	CS, assessed age at menarche and Tanner stages; analyses stratified by ethnic groups	Later pubic hair and breast development associated with higher lead among blacks and Mexican Americans, suggested association among non-Hispanic whites; later menarche associated with higher lead among blacks, suggested association among Mexican Americans and non-Hispanic whites	Selevan et al[112] (2003)
Lead (serum)	US 8- to 16-y-old girls NHANES III (1706)	CS, assessed age at menarche and Tanner stages	Later menarche and pubic hair development with higher lead exposure; no association with breast development	Wu et al[113] (2003)
Lead (serum)	US/Canada Mohawk Nation, girls 10–17 (138)	CS; menarche (yes/no)	Exposure to lead associated with lower likelihood of menarche	Denham et al[102] (2005)

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TABLE 2 Continued

Chemical Exposure (Biospecimen)	Population (Sample Size)	Study Design	Findings	Reference
Mercury (serum)	US/Canada Mohawk Nation, girls 10–17 (138)	CS; menarche (yes/no)	Suggestion of earlier menarche with mercury exposure	Denham et al[102] (2005)
Mirex (serum)	US/Canada Mohawk Nation, girls 10–17 (138)	CS; menarche (yes/no)	No association	Denham et al[102] (2005)
PCBs (serum)	US/Canada Mohawk Nation, girls 10–17 (138)	CS; menarche (yes/no)	4 potentially estrogenic PCB congeners (52, 70, 101+90, and 187) significantly associated with a greater probability of having reached menarche	Denham et al[102] (2005)
PCBs (maternal blood, cord blood, and placenta averaged; breast milk)	US, North Carolina boys and girls (594)	C; assessed menarche, Tanner stages by annual questionnaire	Boys: no association; girls: suggestion of earlier breast and pubic hair development with high transplacental, suggestion of earlier pubic hair development with lactational exposure	Gladen et al[97] (2000)
PCBs (maternal serum)	US, Michigan girls aged 5–24 (256)	CS; assessment of Tanner stages; recall of age at menarche in postmenarchal girls	No association	Blanck et al[95] (2000)
PCBs (cord blood)	Faroe Islands boys (175)	C/CS; genital anomalies at birth, examination at age 14 for Tanner stage, testicular size, spermaturia, and serum hormones	No significant associations; suggestion of higher testosterone with higher PCB exposure	Mol et al[103] (2002)
PCBs (serum; congeners 138, 153, and 180)	17-y-old Belgium boys (78) and girls (120) from polluted and nonpolluted areas	CS; assessment of Tanner stage by examination and testicular volume	Boys: high exposure to PCB 138 less likely to have reached highest stage of genital development, high PCB 153 less likely to have reached highest stage of pubic hair; girls: no associations	Den Hond et al[106] (2002)
PCBs/PCDFs	Taiwan, girls aged 13–19 exposed to contaminated oil (Yucheng) in utero (27) and controls (21)	C; recalled age at menarche, menstrual cycle characteristics, serum hormones	No association with age at menarche; exposed girls reported shorter cycle length and more irregular cycles, exposed girls had higher levels of estradiol and FSH	Yang et al[104] (2005)
PCBs/PCDFs	Taiwan, boys (mean age: 12.3) exposed to contaminated oil (Yucheng) in utero (61) and controls (60)	C/CS; Tanner stages by exam, testicular size, serum hormones	No association with Tanner stage or testicular size; some differences in hormone levels in boys ≥13 years	Hsu et al[105] (2005)
PCBs (estimated maternal serum PCBs at conception)	US, Michigan daughters of women who consumed Great Lakes fish (151)	C; recalled age at menarche	No association	Vasiliu et al[98] (2004)
PCBs (serum congeners)	US/Canada Mohawk Nation, girls 10–17 (138)	CS; menarche (yes/no)	Exposure to estrogenic congeners (52, 70, 90, 101, 187, geometric mean) associated with greater likelihood of menarche; no association with other congener groups	Denham et al[102] (2005)
Phthalates (serum)	Puerto Rico (41 PT cases, 35 controls)	Case control	Serum phthalate (primarily DEHP) significantly higher in cases than controls	Colon et al[109] (2000)

CS, cross-sectional study; C, cohort study; CS/C cross-sectional assessment within a cohort; CALUX, chemically activated luciferase gene expression; PBB, polybrominated biphenyl; NHANES III, Third National Health and Nutrition Examination Survey; PCDFs, polychlorinated dibenzo-furans; PT, premature thelarche.

Germaine M. Buck Louis, et al. *Pediatrics* 2008;121;S192-S207

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MiniReview

Endocrine Disruptors and Abnormalities of Pubertal Development

Greet Schoeters[1,2], Elly Den Hond[1], Willem Dhooge[4], Nik van Larebeke[3] and Marike Leijs[5]

[1]Vlaamse Instelling voor Technologisch Onderzoek (VITO), Environmental Toxicology Unit, Mol, Belgium, [2]Department of Biomedical Sciences, University of Antwerp, Wilrijk, Belgium, [3]Study Centre for Carcinogenesis and Primary Prevention of Cancer, Department of Radiotherapy, Nuclear Medicine and Experimental Cancerology, Ghent University Hospital, Ghent, Belgium, [4]Department of Internal Medicine (Endocrinology), Ghent University Hospital, Ghent, Belgium, and [5]Ecobaby Foundation and Emma Children's Hospital, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands

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Table 1.

Epidemiological studies investigating the relationship between perinatal exposure and pubertal development.

Compound	Study area	Study population	Methods	Main findings	Reference
DDE PCBs	Michigan angler cohort of fish eating mothers with serum DDE levels at time of pregnancy up to 25 μg/l	151 girls	Retrospective study Telephone interviews *In utero* exposure calculated from maternal serum levels	Reduced age at menarche by 1 year associated with an increase in *in utero* DDE exposure of 15 μg/l	[23]
DDE PCBs	North Carolina cohort with DDE concentrations up to 4 μg/g fat	316 girls 278 boys	Prospective study Mail questionnaires Concentrations in mothersmilk and maternal serum	No association with pubertal stages	[24]
PBBs	Michigan food chain contamination	327 girls	Prospective study Physical examination *In utero* exposure extrapolated from maternal serum levels at the time of the accident	Earlier age at menarche and earlier pubic hair stage in breastfed girls with *in utero* PBB exposure above 7 ng/g serum	[28]
PCBs	Faroese birth cohort	196 boys	Prospective study Clinical and physical examination Concentrations in cord blood	No effect on pubertal stages or testicular volume	[29]
PCBs PCDFs	Yucheng	55 boys	Prospective study Clinical and physical examination Maternal serum levels	Pubertal delay	[30]

DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; PBB, polybrominated biphenyl; PCB, polychlorinated biphenyl; PCDF, polychlorinated dibenzofuran.

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Table 2.

Epidemiological studies investigating the relationship between pubertal exposure and pubertal development.

Compound	Study area	Study population	Methods	Main findings	Reference
DDE	Precocious puberty patients (Belgium)	26 immigrant girls and 15 native Belgian girls	Patients study Interviews/physical examination Serum measurements	High levels of plasma DDE in immigrant girls (1.04–1.2 μg/l) compared to Belgian native controls (<0.01 ng/ml)	[20]
PCBs Dioxin measured by CALUX	One rural and two urban villages in Belgium	80 boys and 120 girls (17–18 years old) Mean serum PCB levels: 190 (girls) and 360 (boys) pmol/g fat Mean serum CALUX levels: 29 (girls) and 35 (boys) pg Teq/g fat	Cross sectional study Physical examination Pubertal serum levels	Retarded pubertal development associated with higher PCB exposure in boys Retarded breast development associated with higher dioxin levels in girls	[27]
Dioxins	Seweso	282 girls exposed pre-pubertal	Archived serum levels from time of the accident and extrapolated to age at menarche	No effect on age at menarche	[33]
Lead	NHANESIII cross sectional study	2186 girls	Cross sectional study Physical examination Blood lead levels	Delayed pubertal development (breast and pubic hair stage), delayed age at menarche associated with bloodlead >3 μg/dL	[34]
Lead	NHANESIII cross sectional study	1235 girls (0.7–21.7 μg/dl blood lead)	Cross sectional study Physical examination Blood lead levels	Delayed attainment of menarche and pubic hair growth	[35]
Endosulfan	Indian village with high levels of endosulfan used as pesticide	117 boys with serum endosulfan levels of 7.6 ng/g/90 controls with serum levels of 1.4 ng/g	Cross sectional study Physical examination Serum levels	Delayed sexual maturation (tanner stages)	[36]
Phthalates	Puerto Rico	41 patients with premature breast development/35 controls	Case control study Physical examination Serum analysis	Higher levels of DEHP (average of 450 ng/ml) and MEHP (average of 3 ng/ml) in serum of patients (p.p.b. range)	[39]

CALUX, chemically activated luciferase expression; DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; DEHP, di(2-ethylhexyl)phthalate; MEHP, mono-(2-ethylhexyl)phthalate; PCB, polychlorinated biphenyl.

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Endocrine Disruptors and Abnormalities of Pubertal Development

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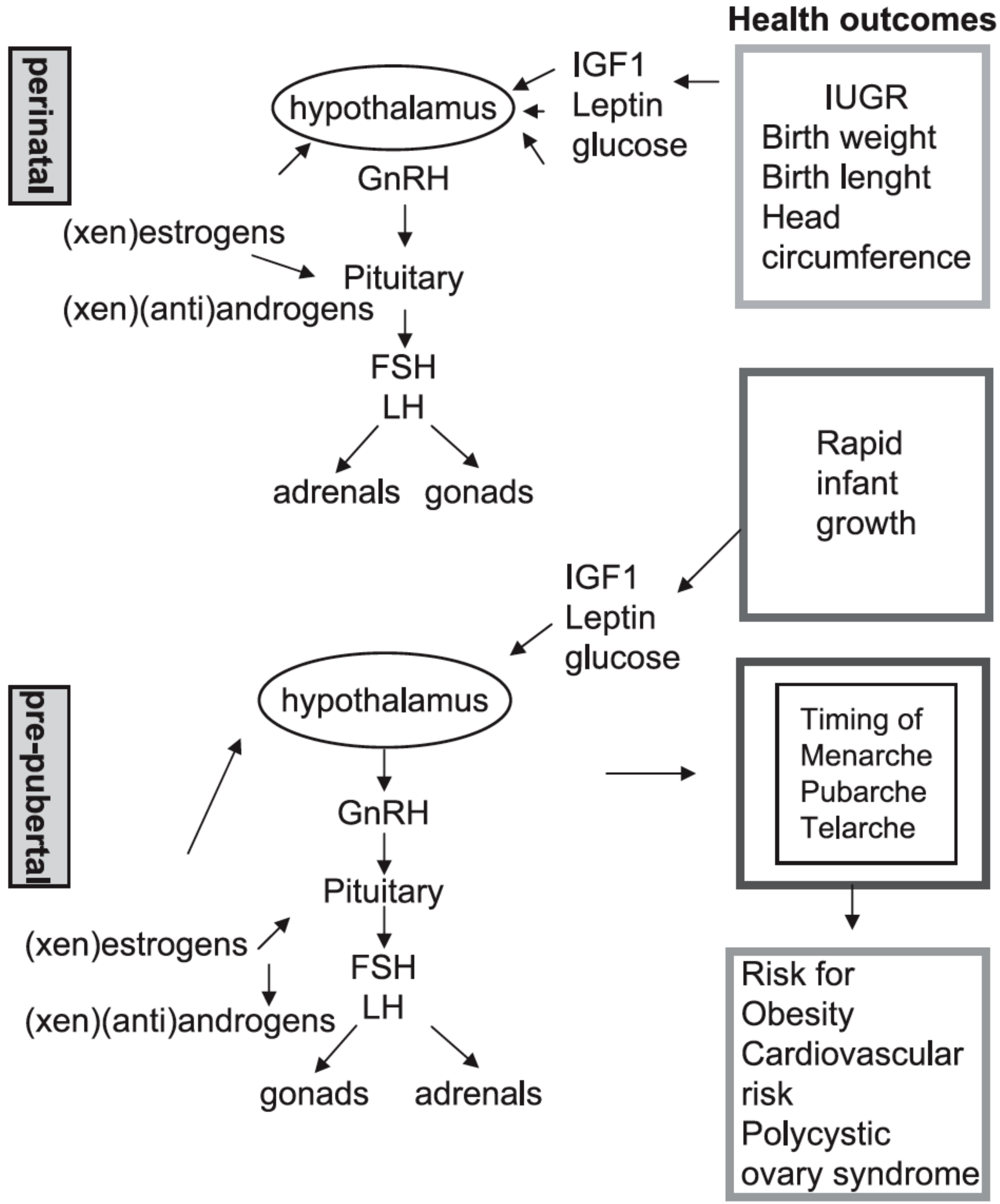

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Phthalates may promote female puberty by increasing kisspeptin activity

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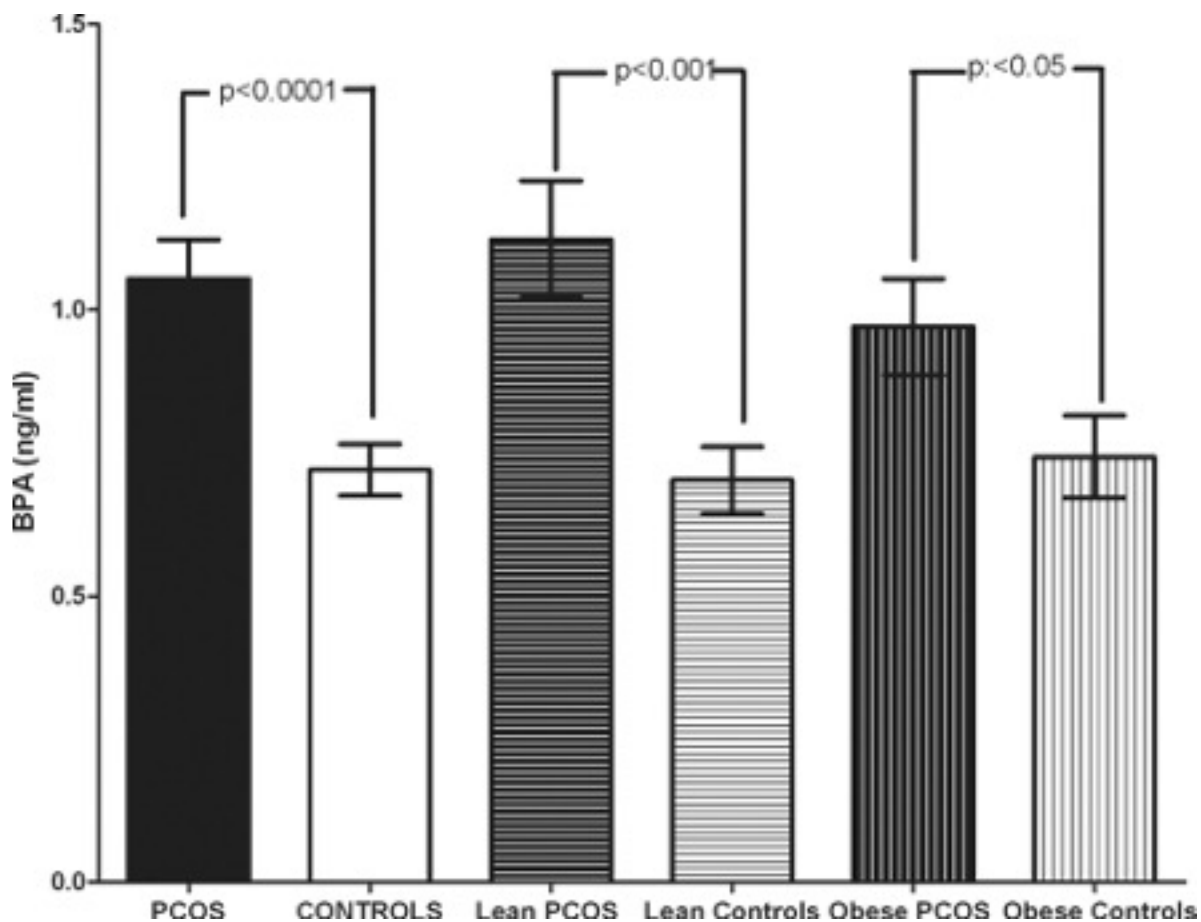
2013 Chen PP Phthalates Kisspeptin

Polycystic Ovary Syndrome and EDCs



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Review

Epigenetic regulation of female puberty

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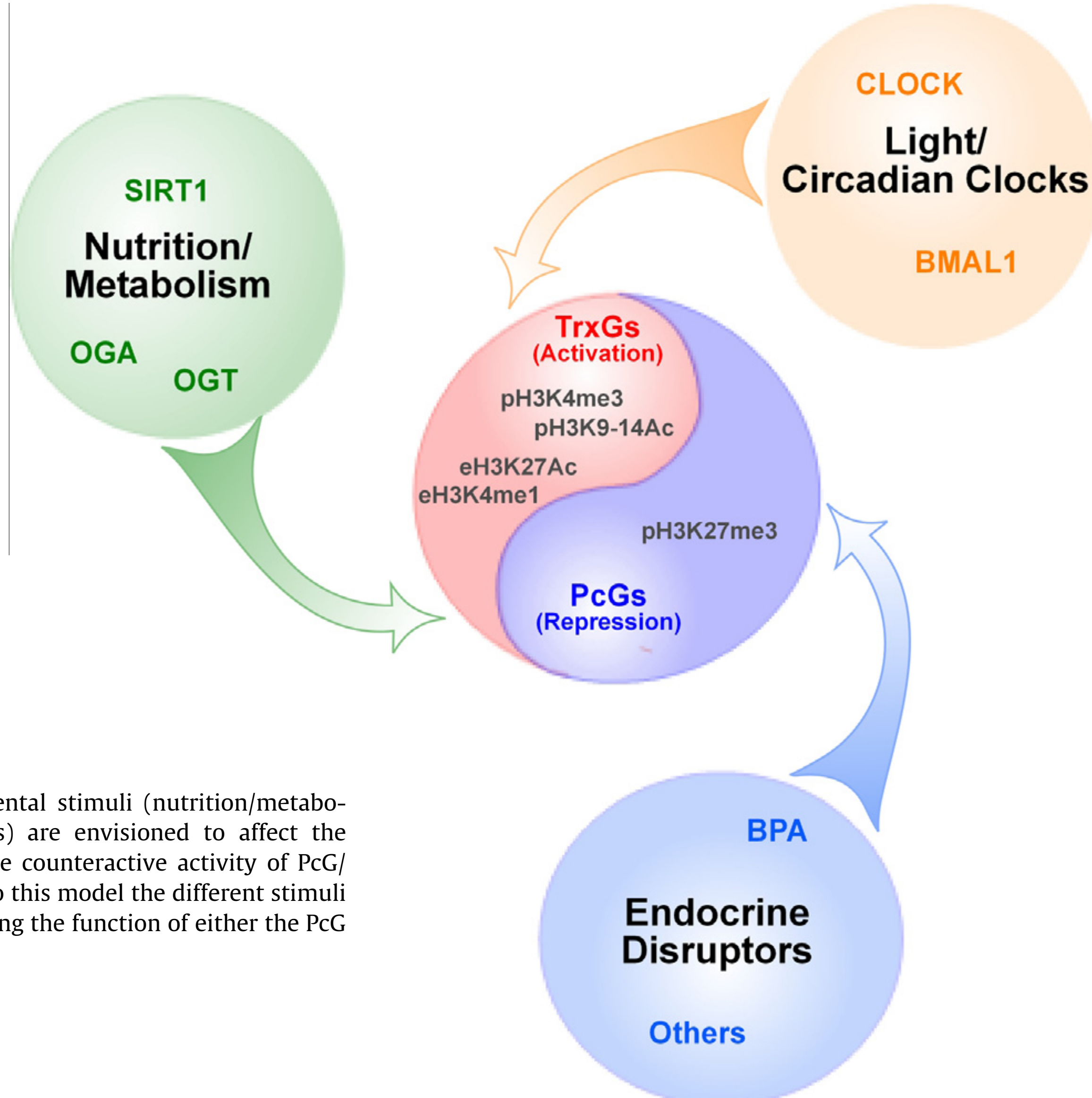
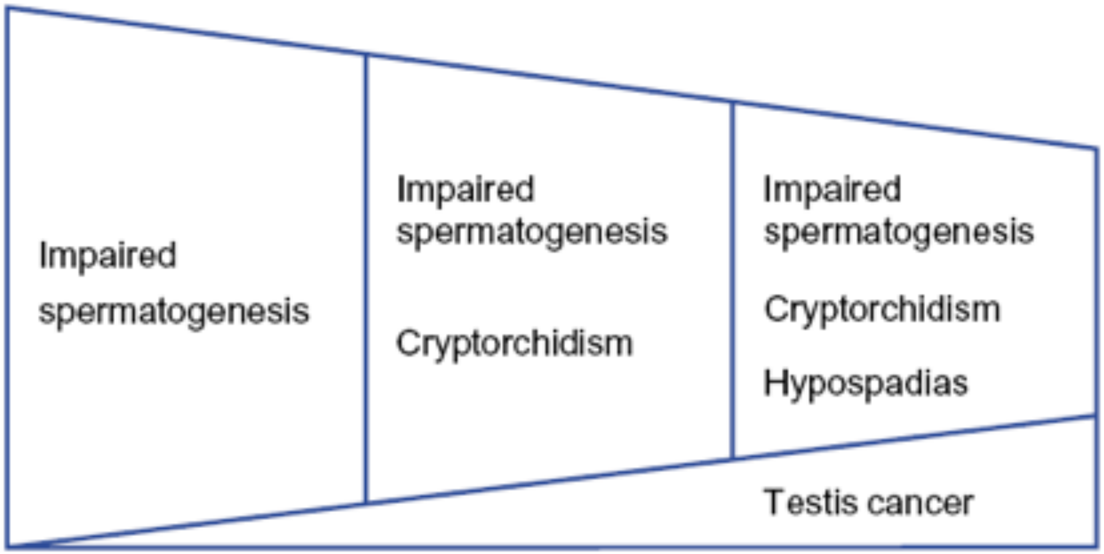


Fig. 6. Different external and internal environmental stimuli (nutrition/metabolism, light/circadian clocks, endocrine disruptors) are envisioned to affect the timing and progression of puberty by altering the counteractive activity of PcG/TrxG-mediated epigenetic machinery. According to this model the different stimuli depicted can affect the time of puberty by modifying the function of either the PcG or TrxG complex or both.

2014 Lomniczi Epigenetics Puberty

TDS: clinical signs variability & hystological findings



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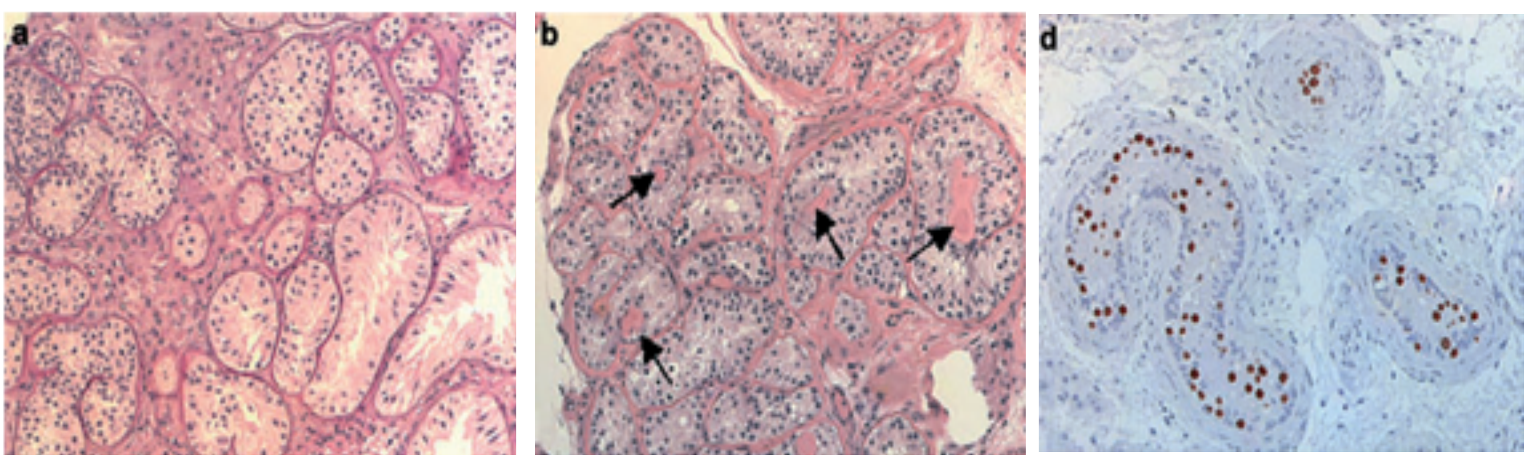
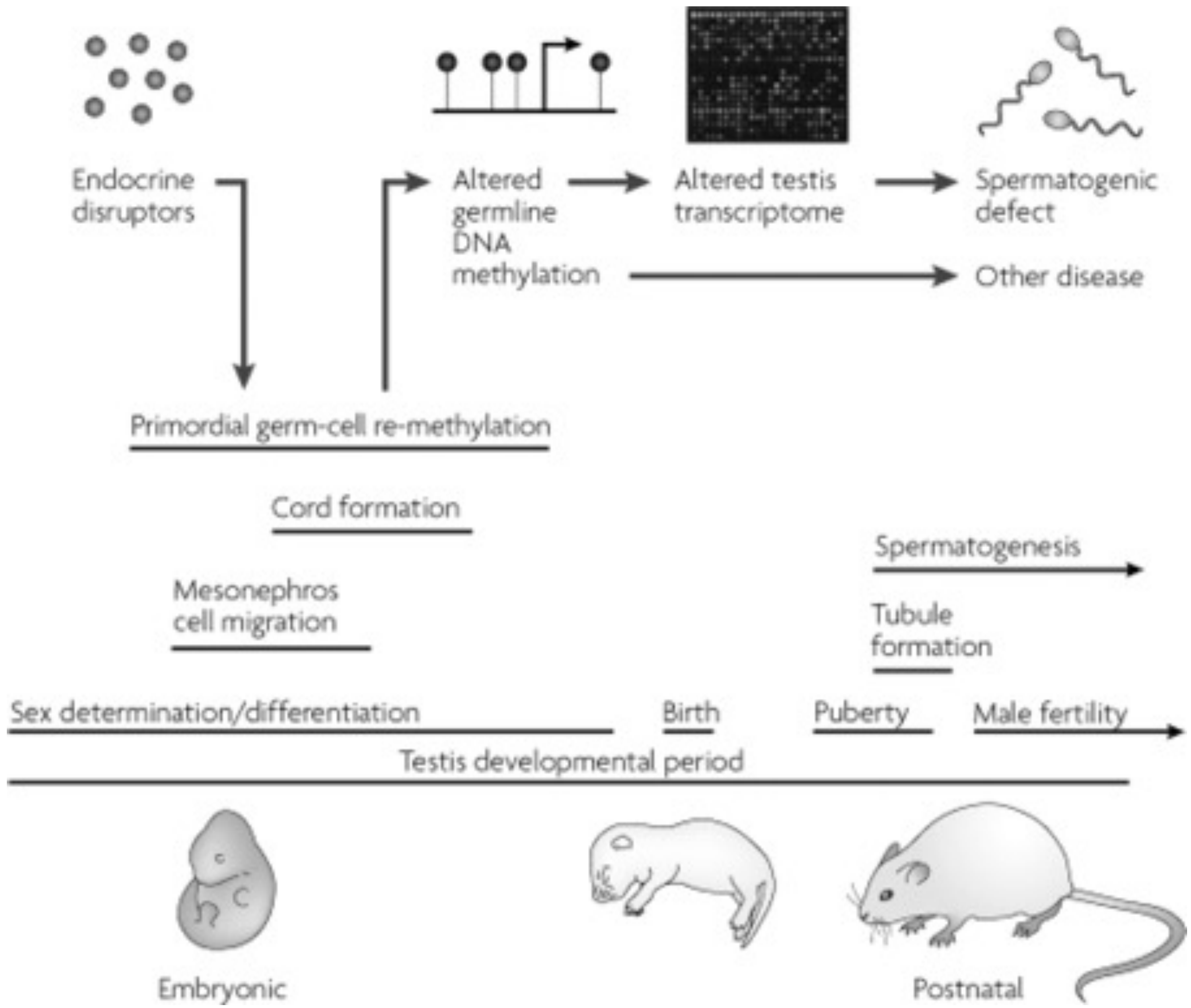


a & b = TDS
d = In Situ Carc.

FIG. 14.

A model for endocrine-disruptor-induced epigenetic transgenerational disease.



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ENDOCRINE REVIEWS

J. Endocrinol. Invest. 28: 589-594, 2005

Puberty onset in Northern Italy: A random sample of 3597 Italian children

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ABSTRACT. Entering puberty is one of the most important milestones in life. Studies from around the world have shown that age of pubertal changes onset can vary with race and ethnicity, environmental conditions, geographical location and nutrition. In the last century, the onset of puberty progressively shifted back towards younger ages in several European countries, with a levelling off in the last decades. The aim of our study was to describe the prevalence of secondary sexual characteristics in a group of children living in Northern Italy comparing them with the percentile values published by Tanner in 1976. We enrolled 3496 children drawn from public schools and evaluated height, weight and pubertal stages. The analysis of our data evidenced that the 50th percentile age of puberty onset in both sexes decreased by about 1 yr compared to data published by Tanner. Mean body mass index (BMI) z-score was significantly higher (p=0.01) in pubertal than in pre-pubertal girls, on the contrary it was higher (p=0.005) in pre-pubertal than in pubertal boys. In conclusion, our study found that girls and boys of our region are beginning pubertal development about 1 yr earlier than Tanner's British population. Taking into consideration the 3rd percentile age for Tanner's breast stage 2 in girls and testicular volume (TV) of 4 ml in boys, the current internationally used cut-off age for precocious puberty, i.e. 8 yr for girls and 9 yr for boys, can be maintained in our population.
(J. Endocrinol. Invest. 28: 589-594, 2005)